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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of: Aberg *et al.*

Application No.: 09/447,218 Group Art Unit: 1623

Filed: November 23, 1999 Examiner: CRANE

For: METHODS FOR TREATING URTICARIA USING DESCARBOETHOXYLORATADINE

Attorney Docket No.: 4821-362

BRIEF ON APPEAL FEE TRANSMITTAL

Box PAI
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

An original and two copies of the applicant's Brief on Appeal in the above-entitled application are submitted herewith. The item(s) checked below apply:

- ☒ The Brief filing fee is $310.00.
- ☐ Applicant has qualified for the 50% reduction in fee for an independent inventor, nonprofit organization or small business concern and the Brief filing fee is $155.00.

The Brief filing fee is:

- ☒ Required.
- ☐ Not required (Fee paid in prior appeal).

Please charge the required Brief filing fee to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Respectfully submitted,

Date: November 8, 2001

45,479
Max Bachraeh (Reg. No.)

For: Stanton T. Lawrence, III (Reg. No. 25,763)

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Enclosures

#17
2 of 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Aberg *et al.*

Application No.: 09/447,218 Group Art Unit: 1623

Filed: November 23, 1999 Examiner: E. CRANE

For: METHODS FOR TREATING URTICARIA USING DESCARBOETHOXYLORATADINE

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BRIEF ON APPEAL

Box PAI
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Pursuant to the provisions of 37 C.F.R. § 1.191 and § 1.192, an appeal is taken herein from the final rejection dated December 22, 2000, which rejects claims 34-40, 48, and 49 of this application.[1] Appellants submit herewith: (a) an original and two copies of this Appeal Brief; (b) three copies of each Exhibit cited in the Appeal Brief; and (c) a Petition for Extension of Time with provision for the required fee.

REAL PARTY IN INTEREST

The real party of interest is the assignee of the above-identified application: Sepracor Inc.

RELATED APPEALS AND INTERFERENCES

Appellants and their legal representatives hereby submit that they are not aware of any appeal or interference which directly affects, will be directly affected by, or will

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[1] News claims 41 and 42 were submitted in an Amendment filed on April 23, 2001. These claims have been renumbered as claims 48 and 49 pursuant to 37 C.F.R. § 1.126.

have a bearing on the Board's decision in this appeal. However, an appeal is pending is connection with parent application no. 09/039,260.

STATUS OF THE CLAIMS

Claims 34-40, 48, and 49 of this application are under final rejection and are the subject of this appeal. Claims 1-33 and 41-47 were previously canceled without prejudice. Appellants timely filed a "Notice of Appeal from the Primary Examiner to the Board of Patent Appeals and Interferences" on June 8, 2001. The appealed claims are presented in Appendix A attached hereto.

STATUS OF AMENDMENTS

Subsequent to the December 22, 2000 final Office Action, an amendment under 37 C.F.R. § 1.116 was filed on April 23, 2001. The Examiner indicated that the amendment will be entered upon the filing of a Notice of Appeal and an Appeal Brief. Thus, the claims as presently pending are as set forth in Exhibit A.

SUMMARY OF THE INVENTION

The invention as recited by the claims on appeal encompasses a method of treating urticaria in a human, which comprises administering to a human in need thereof a therapeutically effective amount of descarboethoxyloratadine (DCL) or a pharmaceutically acceptable salt thereof.

At the time the invention was made, DCL was believed to be the major metabolite of the commercially available, non-sedating antihistamine, loratadine (sold as Claritin®). *See* Specification at page 1, lines 5-10. Also at that time, loratadine and other non-sedating antihistamines, such as astemizole and terfenadine, had been known to cause severe adverse side-effects, including ventricular fibrillation and cardiac arrhythmias. *See* Specification at page 3, lines 22-29. Furthermore, loratadine was reported to possibly induce tumor promotion. *See* Specification at page 4, lines 19-25. However, the invention encompasses the use of DCL to treat disorders, while reducing or avoiding adverse effects exhibited by other non-sedating antihistamines.

Comparative tests performed on DCL and loratadine indicated that DCL is approximately 20 fold more potent at histamine receptors than loratadine in reducing

histamine induced guinea pig icum contractions. *See* Specification at Page 22, Table 2. DCL was also found to have a 14 fold greater affinity than loratadine for histamine H-1 receptors. Test results also demonstrated a higher potency of DCL over loratadine for inhibition of histamine-induced contractions of guinea pig ileum. *Id* at Page 23, Table 3. Surprisingly, *in vitro* testing on fresh spleen cells indicated that DCL was 5-7 fold less active than loratadine at promoting tumor growth. *Id* at Page 24, Table 4.

ISSUE ON APPEAL

The sole issue presented by this appeal is: whether the rejection under 35 U.S.C. § 103(a) of claims 34-40 and 48-49 over Berkow *et al.*, Merck Manual of Diagnosis and Therapy, 16th Ed., (Merck and Co., Rahway, NJ: May 1992); pp. 332-334 in view of U.S. Patent No. 4,659,716 can be maintained despite the lack of the legally required suggestion of the invention by the cited references, despite the teaching away found in the cited references, and despite the showing of unexpected results in the application.[2]

GROUPING OF CLAIMS

Claims 34-40 and 48-49 stand or fall together.

REFERENCES RELIED UPON BY THE EXAMINER

Primary:[3] U.S. Patent No. 4,659,716 ("the '716 patent" or "Villani," submitted herewith as Exhibit B), which issued on April 21 1987, discloses a genus of compounds comprising 7- and 8-(halo or trifluoromethyl)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridines, as potential antihistaminic agents. The '716 patent does not disclose or suggest treating urticaria with any compound, much less treating urticaria with DCL. Therefore, the rejection of the pending claims under § 103 is legally improper.

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[2] Appellants maintain that the cited references do not establish a *prima facia* case of obviousness even in the absence of the teaching away and unexpected results as will be described herein.

[3] Despite the wording of the rejection, the Examiner has stated in the final Action on page 5 that Villani is the primary reference. In either case the combination does not render the claims *prima facia* obvious as demonstrated herein.

Secondary: Berkow *et al.*, Merck Manual of Diagnosis and Therapy, 16th Ed., (Merck and Co., Rahway, NJ: May 1992, pp. 332-334) ("Berkow," submitted herewith as Exhibit C) merely states that symptoms of acute urticaria *usually* can be relieved with oral first generation anti-histamines, such as diphenhydramine, hydroxyzine, or cyprohependine. Berkow not only fails to teach the use of second generation antihistamines against urticaria, but also teaches away from the invention, in part, by teaching that urticaria can be caused by drugs.

ARGUMENT

Appellants request that the Board of Patent Appeals and Interferences ("the Board") reverse the Examiner's rejection of the pending claims. As discussed below, the Examiner has erred not only in improperly combining the Berkow and Villani references but also in failing to appreciate that the appealed claims can be distinguished over that combination. Moreover, the Examiner ignores the teaching away in the art and Appellants showing of unexpected results.

I. THE LEGAL REQUIREMENTS FOR ESTABLISHING A *PRIMA FACIA* CASE OF OBVIOUSNESS

As the Board is well aware, three basic criteria must be met to establish a case of *prima facie* obviousness. First, there must have been at the time of the invention a motivation to combine the references cited. *In re Jones,* 958 F.2d 347 (Fed. Cir. 1992); *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988) (holding that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves on in the knowledge generally available to one of ordinary skill in the art). Second, the alleged prior art must teach or suggest all of the limitations of the claims alleged to be obvious. *In re Royka,* 490 F.2d 981 (CCPA 1974) (holding that to establish *prima facia* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art). Third, there must have been at the time of the invention a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (holding that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure); *Amgen, Inc.*

v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-1208 (Fed. Cir.), *cert. denied* 502 U.S. 856 (1991) (holding that to obviousness requires references to show that there was, at the time of the invention, a reasonable expectation of success).

A. THE SUGGESTION OR MOTIVATION MUST BE IN THE ART NOT IN THE APPLICANT'S DISCLOSURE

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). Where claimed subject matter has been rejected in view of a combination of prior art references, a proper analysis under § 103 requires, *inter alia*, consideration of: (1) whether the references would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process, and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

B. THE USE OF HINDSIGHT IS NOT PERMISSIBLE

Hindsight cannot be used to reject a claim as obvious. *In re Sernaker*, 702 F.2d 989, 994 (Fed. Cir. 1983); *In re Rinehart*, 531 F.2d 1048 (CCPA 1976); *In re Imperato*, 486 F.2d 585 (CCPA 1973); *In re Adams*, 356 F.2d 998 (CCPA 1966). Consequently, it is legally improper to select from the prior art the separate components of the inventor's combination, using the blueprint supplied by the inventor. *C.R. Bard Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1352 (Fed. Cir. 1998) citing *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1985) (holding the prior art must suggest to one of ordinary skill in the art the desirability of the claimed combination).

The Federal Circuit has suggested that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or modification to combine prior art references." *Id.* This is because "when prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1142 (Fed. Cir. 1985).

C. THE DISCLOSURE OF A GENUS OF COMPOUNDS DOES NOT IN ITSELF SUGGEST THE USE OF A PARTICULAR COMPOUND WITHIN THAT GENUS

The use of impermissible hindsight is particularly attractive during the examination of chemical and pharmaceutical patent applications when a prior art reference discloses a genus of compounds that encompasses a specific compound recited by the claims. However, it is well settled that "[t]he fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious." *In re Baird*, 16 F.3d 380, 382 (Fed.Cir. 1994) citing *In re Jones*, 958 F.2d 347 (Fed.Cir. 1992). Further, "the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facia* case of obviousness." *In re Baird*, 16 F.3d at 382.

II. THE PENDING CLAIMS ARE NOT OBVIOUS OVER THE CITED REFERENCES

The Examiner rejected claims 34-40 and 48-49 under 35 U.S.C. § 103 as being obvious over Berkow in view of Villani. The Examiner's rejection is summarized in the Office Actions mailed March 23, 2000 on pages 3-4 and December 22, 2000 pages 3-5 as follows:

> Berkow discloses that symptoms of urticaria usually can be relieved with an oral dose of an antihistamine. Villani discloses that DCL and closely related compounds are effective antihistamines with the advantage of low central nervous system (CNS) related side-effects. The findings that (i) Villani's teaching that DCL and related compounds are known to be effective antihistamines; (ii) the teaching by the Applicants that DCL has the expected effect in the treatment of urticaria is predicted by Berkow; and (iii) the failure of Applicants to establish any unexpected results, when taken together establish that the instant claimed subject matter lacks any patentable distinction in view of the noted references. Therefore, the Examiner alleges that the instant claim of treating urticaria by the administration of DCL would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

A. THE CITED REFERENCES DO NOT SUGGEST THE CLAIMED INVENTION

Claims 34-40 and 48-49 are directed to a method of treating urticaria in a human, which comprises administering to said human a therapeutically effective amount of DCL of a pharmaceutically acceptable salt thereof.

The Examiner has the burden under § 103 to establish a *prima facia* case of obviousness. *In re Piasecki*, 745 F.2d 1468, 1471-1472 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Lalu*, 747 F.2d 703, 705 (Fed. Cir. 1984). The Examiner has not met this burden in this case.

The legally required suggestion of each and every element of the pending claims (*i.e.*, a method of treating a specific disorder – urticaria, using a specific compound – DCL, in a specific host – humans) is not present in Villani or Berkow alone or in combination. *Ecolochem, Inc., v. Southern California Edison Company*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) citing *ACS Hosp. Sys., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577 (Fed. Cir. 1984) (holding obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination). Specifically, there is no suggestion in Berkow to use a second generation antihistamine for treating urticaria. Berkow merely states that symptoms of acute urticaria *usually* can be relieved with oral first generation antihistamines, such as diphenhydramine, hydroxyzine, or cyprohependine.[4] Berkow, page 333, ¶ 4. This suggestion with regard to first generation antihistamines suggests nothing about the use of second generation antihistamines. More importantly, Berkow states that when treating urticaria "nonessential drugs" should be stopped, since urticaria itself can be and is commonly caused by adverse drug actions. Berkow, page 333, ¶ 4. At the time of the invention, adverse drug interactions, albeit not urticaria, were known to occur when non-sedating antihistamines were used. *See* Knowles, Canadian Journal Hosp. Pharm., 45: 33, 37 (1992); Simons *et al.*, Lancet, 2: 624

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[4] Such antihistamines are generally considered first generation antihistamines and are believed to be sedating and possess adverse effects, unlike second generation antihistamines. *See Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed.; 1996, pp. 586-591 (Exhibit D).

(1988) (Exhibit E). Thus, Berkow would teach one of ordinary skill *away* from the use of any second generation antihistamines against urticaria. Berkow merely suggests that first generation histamine antagonists having anticholinergic and sedative effects (*e.g.*, diphenhydramine, hydroxyzine, and cyproheptadine) *may* have a beneficial effect on urticaria. However, DCL is not a first generation antihistamine. More significantly, Berkow teaches that urticaria can be caused by adverse drug interactions. At the time of the invention, adverse drug interactions associated with the administration of second generation antihistamines were a concern, thus contradicting any suggestion of their use by Berkow.

Villani merely discloses a class of compounds of the type: 8-(halo)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta-[1,2-b]pyridines allegedly having antihistaminic properties and low central nervous system (CNS) activity indicative of non-sedation.[5] *See* Col. 1, lines 17-38. Villani does not even mention urticaria, nor suggest a treatment thereof.

Clearly, combining the suggestion in Berkow of possibly treating the symptoms of urticaria with a first generation, sedating antihistamine with the general disclosure in Villani of second generation antihistamines does not render the claimed method of treating urticaria *prima facia* obvious. As the Board has asserted in *Ex parte Clapp*, "[t]o support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the Examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Appellants submit that there is neither an express or implicit suggestion of the claimed invention in the references, nor does the Examiner present any convincing reasoning why the claimed invention is obvious. Therefore, the Examiner's rejection must be reversed.

In addition, the mere fact that references *can* be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990) (emphasis added) citing *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) (the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the

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[5] Again, such compounds are distinct in structure and function from first generation antihistamines.

desirability of the modification). In the instant case, there is no such suggestion to combine the references cited by the Examiner.

Even assuming *arguendo* a suggestion or motivation to combine the cited references existed, one of ordinary skill in the art would have no suggestion to use the second generation antihistamine, DCL, to treat urticaria in humans, much less be given a reasonable expectation that DCL would work and work without adverse effects associated with other second generation antihistamines.[6] Thus, Appellants submit that the requisite suggestion or motivation for one of ordinary skill in the art to arrive at the elements of the claimed invention is absent. *In re Oetiker*, 977 F.2d 1443 (Fed. Cir. 1992). Because the suggestion to combine Berkow and Villani is absent from the cited references, the Board should overturn the Examiner's rejection and allow the pending claims.

B. VILLANI ALONE OR IN COMBINATION WITH BERKOW DOES NOT RENDER THE CLAIMS *PRIMA FACIA* OBVIOUS

The Examiner also alleges that Villani discloses a method of treating allergic reactions generically. The Examiner then asserts that because urticaria is a medical name for the skin reaction of an allergic host in contact with an allergen the instant claims are obvious. *See* December 22, 2000 Office Action at page 5.

However, as the Board is well aware, the disclosure of a genus does not by itself render obvious a species within that genus, and that absent the further teaching or suggestion of a species, the disclosure of a large genus does not render obvious a species comprising one of them. *In re Baird*, 16 F.3d at 382 (Fed. Cir. 1994) (a generic formula encompassing a claimed composition did not provide the requisite motivation to select the composition because the reference (a) disclosed a "vast number" of possibilities, and (b) gave as "typical," "preferred," and "optimum" examples that are "different from and more complex than" the claimed composition.). Here, as in *Baird*, Villani does not disclose anywhere in its specification a specific type of allergy or allergic reaction, much less treating the specific disorder urticaria.

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[6] Again, it was well settled at the time of the invention that many second generation antihistamines cause adverse effects including adverse effects resulting from drug-drug interactions, which was a concern in Berkow. Knowles, Canadian Journal Hosp. Pharm., 45: 33, 37 (1992); Simons *et al.*, Lancet, 2: 624 (1988) (Exhibit E).

To be more specific, allergic reactions are defined as local or general reactions of an organism following contact with a specific allergen to which it has been previously exposed and sensitized; allergic reactions are classified into four major types: type I, anaphylactic and IgE dependent; type II, cytotoxic; type III, immune-complex mediated; and type IV, cell-mediated. *See* Stedman's Medical Dictionary, 27th Ed.; M. Spraycar, Editor; Williams & Wilkins, 2000, pp. 1523 (Exhibit F). Thus, the disclosure of Villani to treat an allergic disorder is so broad, that one of ordinary skill in the art could not possibly infer urticaria from such a broad genus, much less a method of using DCL to treat urticaria. *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopaedics, Inc.*, 976 F.2d 1559 (Fed. Cir. 1992) (although a patent's specific claims are subsumed in a reference's generalized disclosure, the disclosure can be "so broad as to be meaningless" and provide no guidance on how to construct a product with the patented invention's beneficial properties).

Given the limitless number of allergic reactions encompassed by Villani and the fact that Villani does not disclose any specific allergies or allergic reactions, the Board must conclude that Villani does not teach or fairly suggest the selection of urticaria, much less the method of treating urticaria with DCL. In other words, Villani's disclosure of treating allergic reactions is so broad as to be meaningless and provides no guidance as to a specific method of treating urticaria, much less a motivation to use DCL to treat urticaria. *See Minnesota Mining & Manufacturing Co.*, 976 F.2d at 1572. As demonstrated above, a combination of Berkow and Villani would merely teach one of ordinary skill in the art to treat urticaria with a first generation sedating antihistamine or to use DCL to treat an unknown generic class of allergic reactions that can encompass literally hundreds of allergic reactions without providing the legally necessary suggestion of treating urticaria.

Thus, the references alone or in combination fail to suggest a method of treating urticaria using DCL.

C. THE PRIOR ART ACTUALLY TEACHES AWAY FROM THE CLAIMED INVENTION

As stated above, Berkow does not provide a reasonable expectation of success in treating urticaria with first generation antihistamines. Berkow teaches away from the use of certain drugs by teaching that urticaria can be caused by drugs or drug-drug interactions. The art, including Berkow, even further teaches away from the claimed invention. It has been reported that hydroxyzine (one of the agents Berkow suggests to treat urticaria) may induce urticaria rather than treat it. *See* Michel *et al.*, Skin Reactions to Hydroxyzine,

Contact Dermatitis, **1997**, *36*, 147-149 ("Michel") (Exhibit G). The Michel reference would therefore at the very least impart confusion in the art, if not refuting the disclosure of Berkow concerning the possible use of antihistamines against urticaria, altogether.

It has also been shown that certain types of urticaria *do not respond* at all to antihistaminic drugs. *See* Parslew *et al.*, Warfarin Treatment of Chronic Idiopathic Urticaria and Angio-Oedema, *Clinical and Experimental Allergy*, **2000**, *30*, 1161-1165 (Exhibit H). Such art is directly contrary to Berkow and must be considered by the Examiner. Indeed, a proper analysis under § 103 requires consideration of the scope and content of the art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). When proper consideration is given to the art as a whole, it is clear that the contention that Berkow suggests that DCL can be expected to treat urticaria is meritless.

Thus, because the very antihistamines suggested by Berkow have been reported to induce urticaria rather than treat it (*See* Michel *supra*), and because it has been shown that certain types of urticaria *do not respond* at all to antihistaminic drugs (*See* Parslew *supra*), the cited art cannot fairly be said to suggest the claimed invention, much less provide the legally required expectation of success. As discussed above, non-sedating antihistamines such as terfenadine, astemizole, and loratadine were believed to cause certain adverse effects at the time of the invention. In particular, they were known to cause cardiac arrhythmias. Indeed, the art reported that such adverse effects were caused or enhanced by drug-drug interactions and thus co-administration of these non-sedating antihistamines with medications that inhibit cytochrome P450 were avoided.[7] *See Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed. 1996, pp. 1607 (Exhibit I). Although second generation antihistamines lack certain adverse effects associated with first generation antihistamines (*e.g.*, anticholenergic activity), these compounds, at the time of the invention, were becoming increasingly disfavored due to their inherent cardiotoxicity.

Finally, the Examiner has failed, but is legally required, to consider the fact that skin reactions to certain second generation antihistamines have been reported, further disfavoring their administration, especially for treating urticaria. *See* McClintock *et al.*, Skin Reactions and Terfenadine, *New Zealand Medical Journal*, **1995**, *108*, 208 (Exhibit J).

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[7] It should be noted that claim 37 recites a method of treating urticaria which comprises administering a therapeutically effective amount of DCL, wherein the interaction between DCL and a drug that inhibits cytochrome P450 is avoided.

Again, when the art is considered asa whole there are several "teachings away" from the invention.

Said another way, one of ordinary skill in the art would not read the suggestion in Berkow "to try" first generation antihistamines as a suggestion to try second generation antihistamines, which are known as a class to have different risks and benefits.[8] Indeed, one of ordinary skill in the art would have no motivation to even try second generation, non-sedating antihistamines to treat urticaria. In fact, the state of the art at the time of the invention actually teaches away from a general use of first or second generation antihistamines to treat urticaria, since it was reported that both classes of antihistamines were either ineffective in treating urticaria or actually induced urticarial outbreaks upon administration. *See* Michel *supra*. *See also* Monroe, Loratadine in the Treatment of Urticaria, *Clinical Therapeutics*, **1997**, *19*, 232-242 (Exhibit K). At the time of the invention the art taught away from using second generation antihistamines to treat urticaria due to the potential for cardiotoxicity and the potential for adverse skin reactions after administration of these antihistamines.

D. UNEXPECTED RESULTS ARE SET FORTH IN THE SPECIFICATION

The Examiner has alleged that the Appellants fail to establish any unexpected results. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (holding one way to rebut a *prima facia* case of obviousness is to make a showing of unexpected results). Appellants respectfully direct the Board to the Example section of the specification. The Examples describe the activity of DCL and its use, while avoiding or reducing adverse effects associated with other second generation antihistamines. This is particularly important in view of the fact that at the time prior to the claimed invention, compounds of the class of non-sedating antihistamines (*e.g.*, loratadine, terfenadine, astemizole) were known to cause or have a potential for severe adverse effects, such as ventricular fibrillation, cardiac arrhythmias, and tumor growth. Such surprising and unexpected benefits encompassed by the claimed invention are sufficient to rebut a *prima facia* case of obviousness. For example, Example 4 illustrates that DCL is 5-7 fold less active than loratadine at promoting tumor growth. *See* Specification at Page 24.

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[8] Appellants point out that even if there was a suggestion to try second generation antihistamines, "obvious to try" is not the proper legal standard. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

Example 5 demonstrates that DCL is less active than terfenadine in inhibiting the cardiac delayed rectifier and thus has a less significant chance of cardiac side-effects. *See* Specification at Pages 24-26. Appellants respectfully request proper consideration of these by the Board and submit that the Examiner's failure to consider this data is reversible error.

Appellants therefore respectfully request reversal of the Examiner's rejection and allowance of the claims.

CONCLUSION

Neither Villani nor Berkow taken alone or in combination suggest a method of treating urticaria, with a second generation antihistamine, much less the specific compound DCL. Neither reference taken alone or in combination provides the required reasonable expectation of successfully arriving at the claimed invention. Indeed, at the time of the invention a reasonable expectation of success could not exist since (a) the state of the art was confused as to what types of drugs were useful in treating urticaria; (b) certain antihistamines were believed to even cause urticaria in some instances (thus teaching away); and (c) second generation antihistamines were known to cause adverse effects including drug-drug interactions (further teaching away). Finally, the specification provides data that is contrary to the Examiner's contention of obviousness.

For any of the reasons stated above, it is respectfully submitted that the final rejections of claims 34-40 and 48-49 under 35 U.S.C. § 103 are in error and warrant reversal by the Board.

Respectfully submitted,

Attorney for Appellants

Date: November 8, 2001

45,479
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Attachments

Exhibit A

Claims on Appeal

34. (Twice Amended) A method of treating urticaria in a human comprising administering to a human in need thereof a therapeutically effective amount of descarboethoxyloratadine (DCL) or a pharmaceutically acceptable salt thereof.

35. (Twice Amended) The method of claim 34, which further comprises reducing or avoiding adverse effects associated with non-sedating antihistamines.

36. The method of claim 34 wherein said human has a higher than normal propensity for or incidence of cancer.

37. (Twice Amended) The method of claim 34, which further comprises avoiding an interaction between descarboethoxyloratadine (DCL) and a drug that inhibits cytochrome P450.

38. (Amended) The method of claim 34 wherein the amount of descarboethoxyloratadine (DCL) administered is from about 0.1 mg to less than about 10 mg per day.

39. (Amended) The method of claim 38 wherein the amount of descarboethoxyloratadine (DCL) administered is from about 0.1 mg to less than about 5 mg per day.

40. (Amended) The method of claim 34 wherein the amount of said descarboethoxyloratadine (DCL) or a pharmaceutically acceptable salt thereof is administered together with a pharmaceutically acceptable carrier.

48. (New) The method of claim 35, wherein the adverse effect is cardiac arrhythmia.

49 (New) The method of claim 35, wherein the adverse effect is tumor promotion.

United States Patent [19]

Villani et al.

[11] Patent Number: 4,659,716

[45] Date of Patent: Apr. 21, 1987

EX B

[54] ANTIHISTAMINIC 8-(HALO)-SUBSTITUTED 6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-b]PYRIDINES

[75] Inventors: Frank J. Villani, Fairfield; Jesse K. Wong, Union, both of N.J.

[73] Assignee: Schering Corporation, Madison, N.J.

[21] Appl. No.: 838,974

[22] Filed: Mar. 12, 1986

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 580,304, Feb. 15, 1984, abandoned.

[51] Int. Cl.[4] A61K 31/445; C07D 401/08

[52] U.S. Cl. 514/290; 546/93

[58] Field of Search 546/93; 514/290

[56] References Cited

U.S. PATENT DOCUMENTS

3,326,924	6/1967	Villani	546/93
3,717,647	2/1973	Villani	546/315
4,282,233	8/1981	Villani	546/93 X

FOREIGN PATENT DOCUMENTS

46-20387	6/1971	Japan	546/93

OTHER PUBLICATIONS

PDR, 1984, pp. 515, 529, 557, 558, 566, 593, 594, 611, 631, 633, 648, 664, 667, 668, 709.

Scrip No. 1026, 8/19/85.

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Primary Examiner—Richard A. Schwartz

Attorney, Agent, or Firm—James R. Nelson; Stephen I. Miller; Richard C. Billups

[57] ABSTRACT

Disclosed are 7- and/or 8-(halo or trifluoromethyl)-substituted-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines and the pharmaceutically acceptable salts thereof, which possess antihistaminic properties with substantially no sedative properties. Methods for preparing and using the compounds and salts are described.

16 Claims, No Drawings

ANTIHISTAMINIC 8-(HALO)-SUBSTITUTED 6,11-DIHYDRO-11-(4-PIPERIDYLIDENE)-5H-BENZO[5,6]CYCLOHEPTA[1,2-B]PYRIDINES

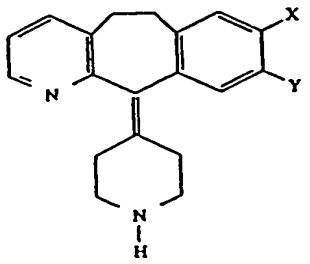
The present application is a continuation-in-part of U.S. application Ser. No. 580,304, filed Feb. 15, 1984, now abandoned, the benefit of which is claimed pursuant to the provisions of 35 U.S.C. 120.

BACKGROUND OF THE INVENTION

U.S. Pat. Nos. 3,326,924, 3,717,647 and 4,282,233 describe certain 11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridines.

SUMMARY OF THE INVENTION

The present invention is directed to compounds having structural formula I:



I

or pharmaceutically acceptable salts thereof, wherein X and Y independently represent H, halo (i.e., fluoro, chloro, bromo or iodo), or trifluoromethyl with the proviso that at least one of X and Y is halo or trifluoromethyl. Particularly, preferred compounds are those wherein X is F and Y is H and wherein X is Cl and Y is H.

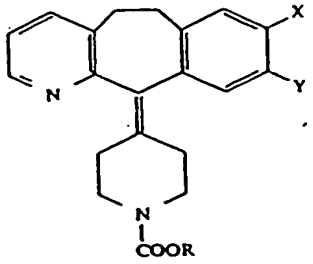
The compounds of the invention have unexpectedly been found to possess advantageous antihistaminic activity and low central nervous system (CNS) activity indicative of non-sedation. The compounds can thus be employed in pharmaceutical compositions in combination with pharmaceutically acceptable carriers and in methods of treating allergic reactions in a mammal.

DESCRIPTION OF THE INVENTION

The compounds of the invention can form salts with pharmaceutically acceptable acids such as hydrochloric, methanesulfonic, sulfuric, acetic, maleic, fumaric, phosphoric and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base form may be regenerated by treating the salt forms with a base. For example, dilute aqueous base solutions may be utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base form differs from the respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but the salts are otherwise equivalent to the respective free base form for purposes of the invention.

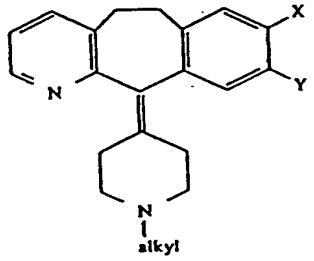
The compounds of the invention and their corresponding salts can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

The compounds of the invention can be prepared by decarbalkoxylation of a compound of the formula II:



II

wherein R is an alkyl group (preferably ethyl) and X and Y are as defined above. The compounds of formula II can be prepared by procedures described in U.S. Pat. No. 4,282,233 from the corresponding N-alkyl (preferably N-methyl) compounds of formula III

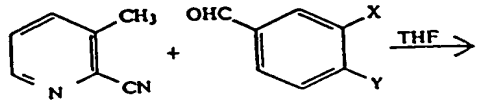


III

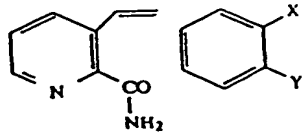
by employing appropriate starting materials having the desired X and Y substituents.

Alternatively, the compounds of the invention can be prepared by dealkylation of compounds of formula III, e.g., by reaction with cyanogen bromide and subsequent hydrolysis of the N-cyano product with, for example, aqueous acid solution to provide the compounds of formula I.

The compounds of formula III can be produced by the procedures described in U.S. Pat. No. 3,326,924 by employing the appropriately X and Y substituted starting materials. For example, 2-cyano-3-picoline of formula IV can be reacted with an appropriate benzaldehyde of formula V in the presence of a strong base such as potassium butoxide to give an ortho-phenethenyl pyridine carboxamide of formula VI

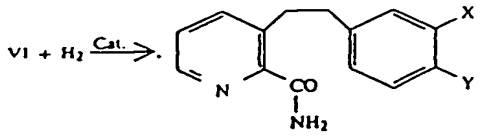


IV V



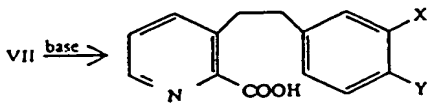
VI

which is then hydrogenated, e.g., by employing a noble metal on carbon catalyst such as palladium or platinum on carbon, to the corresponding ortho-phenethyl pyridine carboxamide of formula VII



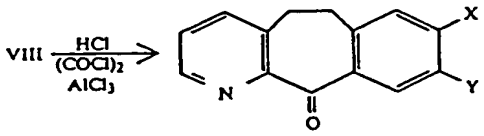
VII

which in turn is hydrolyzed, e.g, with base such KOH, to the otho-phenethyl pyridine carboxylic acid of formula VIII



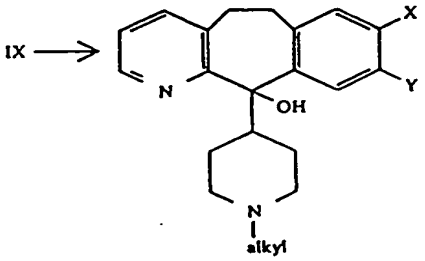
VIII

The compound of formula VIII can be cyclized, e.g., with oxalyl chloride and aluminum trichloride, to a compound of formula IX



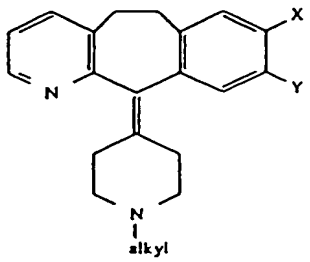
IX

which is reacted with, for example, a Grignard reagent prepared from a 4-halo-N-alkyl-piperidine to produce the compound of formula X



X

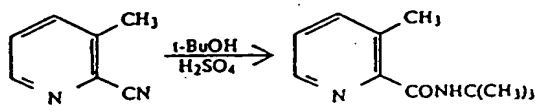
which in turn is dehydrated, e.g., by acid such as polyphosphoric acid or sulfuric acid, to the compound of formula III:



III

The compound of formula IX may also be reacted with Na in liquid NH_3 and a 4-halo-N-alkyl-piperidine to produce the compound of formula X.

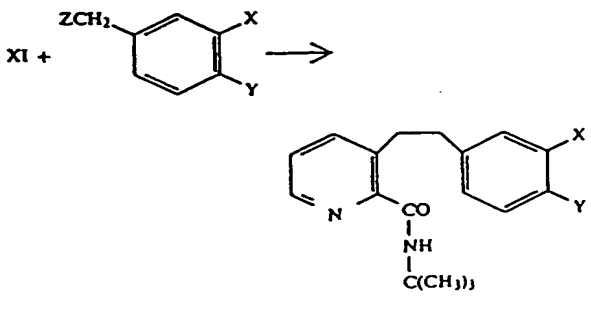
In an alternative method 2-cyano-3-methylpyridine can be reacted in a Ritter reaction with a tertiary butyl compound in an acid such as concentrated sulfuric acid or concentrated sulfuric acid in glacial acetic acid to form a compound of formula XI



IV XI

Suitable tertiary butyl compounds include, but are not limited to, t-butyl alcohol, t-butyl chloride, t-butyl bromide, t-butyl iodide, isobutylene or any other compound which under hydrolytic conditions forms t-butyl carboxamides with cyano compounds. The temperature of the reaction will vary depending on the reactants, but generally the reaction is conducted in the range of from about 50° C. to about 100° C. with t-butyl alcohol. The reaction may be performed with inert solvents but is usually run neat.

The product of the Ritter reaction (formula XI) can be reacted with an appropriate 3 and/or 4-halo or trifluoromethyl-substituted benzyl halide, in the presence of a base to form the compound of formula XII

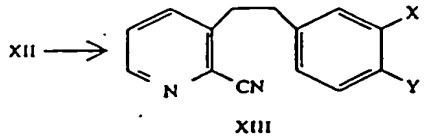


XII

wherein Z is chloro, bromo or iodo. Examples of appropriate benzyl halides include, but are not limited to, 3-chloro-benzyl chloride, 3-fluoro-benzyl bromide, 3,4-dichloro-benzyl chloride, 4-fluoro-benzyl chloride, 3-trifluoromethyl-benzyl chloride, 3-bromobenzyl chloride, etc. Any suitable base can be employed e.g., an alkyl lithium compound such as n-butyl lithium in tetrahyrofuran (THF). Preferably the base has a pK_a of greater than 20 and more preferably greater than 30.

This reaction can be conducted at any suitable temperature, e.g., temperatures of from about −78° C. to about 30° C., preferably from about −40° C. to about −30° C. The reaction can be performed in any suitable inert solvent such as THF, diethyl ether, etc.

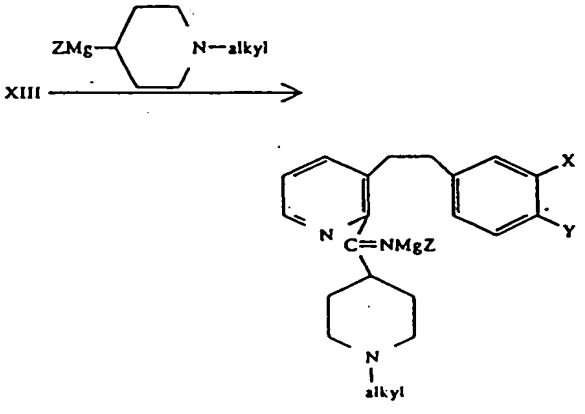
The tertiary-butyl amide of formula XII can be converted to the cyano compound of formula XIII



XIII

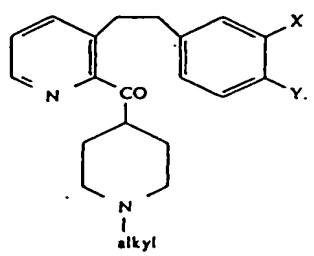
by the use of a suitable dehydrating agent such as $POCl_3$, $SOCl_2$, P_2O_5, toluene sulfonyl chloride in pyridine, oxalyl chloride in pyridine, etc. This reaction can be performed in the absence of or with a co-solvent such as xylene. The dehydrating agent such as $POCl_3$ is employed in equivalent amounts or greater and preferably in amounts of from about 2 to about 15 equivalents. Any suitable temperature and time can be employed for performing the reaction, but generally heat is added to speed up the reaction. Preferably, the reaction is performed at or near reflux.

The cyano compound of formula XIII can then be reacted with a Grignard reagent prepared from the appropriate 1-alkyl-4-halopiperidine. This reaction is generally performed in an inert solvent such as an ether, toluene or tetrahydrofuran. This reaction is performed under the general conditions for a Grignard reaction, e.g., at temperatures of from about 0° C. to about 75° C. The resulting compound of formula XIV



XIV

(wherein Z is again chloro, bromo or iodo) is hydrolyzed, e.g., by reaction with aqueous acid such as aqueous HCl to prepare the corresponding ketone of formula XV

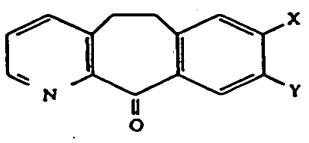


XV

The compound of formula XV can be ring-closed to form the desired cycloheptene ring system by treating the compound XV with a super acid having a Hammett acidity function of less than about minus 12, e.g., minus 13, minus 14, etc., to produce a compound of formula III. This measure of acidity is defined in Hammett, Louis P., and Deyup, Alden J., *Journal of the American Chemical Society*, Vol. 54, 1932, p. 2721. Suitable super acids for this purpose include, for example, HF/BF_3, CF_3SO_3H, CH_3SO_3H/BF_3, etc. The reaction can be performed in the absence of or with an inert co-solvent such as CH_2Cl_2. The temperature and time of the reaction vary with the acid employed. For example, with HF/BF_3 as the super acid system the temperature may be controlled so as to minimize side reactions, such as HF addition to the double bond of the rings. For this purpose, the temperature is generally in the range of from about +5° C. to −50° C., preferably from about −30° C. to −35° C. With CF_3SO_3H as the super acid system, the reaction may be run at elevated temperatures, e.g., from about 25° C. to about 150° C. and at lower temperatures but the reaction then takes longer to complete.

Generally the super acid is employed in excess, preferably in amounts of from about 1.5 to about 30 equivalents. For example, with HF/BF_3 as the super acid system the molar ratio of HF to the compound of formula XV in the reaction mixture is preferably from about 30 to about 1.5, more preferably 2.5 to 1.5. In such system, the molar ratio of BF_3 to the compound of formula XV in the reaction mixture is preferably from about 15 to about 0.75, more preferably from about 1 to about 0.75.

As another alternative, a compound of formula XII above can be cyclized by use of super acid such as CF_3SO_3H or HF/BF_3 to produce a compound of formula IX.



IX

The compounds of formula IX may then be converted to the desired compounds of the invention as described above.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubi-

lizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 5 to about 20 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethyl-cellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and therey solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol and the like as well as mixtures thereof. Naturally, the solvent utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

The composition of the invention may also be deliverable transdermally, e.g., with a transdermally acceptable carrier. The transdermal compositions can take the form of creams, lotions and/or emulsions, can be included in an appropriate adhesive for application to the skin or can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the transdermally acceptable composition is utilized to prepare a "reservoir type" or "matrix type" patch which is applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of formula I through the skin. Most preferably, the patch of the invention will be worn for a period of about 24 hours and provide a total daily dosage of about 1 mg to about 40 mg, preferably from about 5 mg to about 10 mg, of a compound of the invention. The patch may then be replaced if necessary with a fresh patch, thereby providing a constant blood level of a compound of formula I to the patient in need thereof.

The utilization of this new transdermal dosage form and its prescribed regimen will provide the advantages described above. Other frequencies of dosage application are anticipated, for example, a once every 3 day frequency or a once every 7 day frequency. Although a once a day dosage regimen may be preferred, it is not intended that the invention be limited to any particular regimen.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet or tablet itself or it can be the appropriate number of any of these packaged form.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 1000 mg according to the particular application. The compositions can, if desired, also contain other therapeutic agents, such as decongestants.

The dosages may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The compounds of the invention possess antihistaminic properties. The antihistaminic properties of these compounds may be demonstrated by use of standard pharmacological testing procedures. For example, the ability of the compounds to reduce histamine-induced paw edema in mice may be measured by use of the following method.

Male CF_1 mice, 25–30 g, are housed under conditions of controlled temperature and humidity with a 12 hour dark/light cycle. Food and water are allowed ad libitum. The mice are randomly assigned to the treatment groups. One hour after treatment with a compound of the invention or vehicle, the mice are lightly anesthetized with ether. The left hind paw of each mouse serves as a control and is injected with 25 μl of isotonic saline. The right hind paw serves as the experimental

paw and is injected with 25 μl of isotonic saline containing 13 μg histamine dihydrochloride. Thirty minutes later the mice are killed by cervical dislocation and both hind paws of each mouse are removed by cutting at the tarsal joint. The weight of each paw is recorded and the difference in weight between the compound-treated and the placebo-treated groups is evaluated using Student's "t" test. The ED_{50} values (the dose causing 50% inhibition of histamine-induced edema) and 95% confidence limits are determind by the Linear Least Square Dose-Response method [Brownlee, K. A., "Statistical Theory And Methodology In Science and Engineering", 2nd Ed., J. Wiley and Sons, New York, 1965, pp. 346–349]. The compounds of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (Compound A) and 8-fluoro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (Compound B) were tested by this procedure with the results shown in Table 1 below:

TABLE 1

Treatment	Oral Dose mg/kg	No. of Animals	Increased Paw Weight (mg) Mean	% Inhibition	Oral ED_{50} (mg/kg)
Placebo	—	7	22.3	—	—
Compound A	0.03	8	19.9	11	
	0.1	7	13.0	42	
	0.3	8	6.1	73	0.15
	1.0	8	2.5	89	
Compound B					<3

Compounds A and B were also tested for antihistaminic activity by the procedures set forth in paragraph A below and for CNS activity by the procedures set forth in paragraphs B, C, and D below.

A. Prevention of histamine-induced lethality in guinea pigs. Compounds A and B were evaluated for their ability to protect female albino guinea pigs (250–350 g) against death induced by the intravenous injection of histamine dihydrochloride at 1.1 mg/kg, which is approximately twice the LD_{99}. Doses of the antagonists were administered orally to separate groups of fasted animals 1 hour prior to the challenge with histamine and protection from death recorded for 30 minutes after histamine. ED_{50} values were determined for each drug by prohibit analysis.

B. Antagonism of Physostigmine Lethality. The physostigmine-induced lethality test used was a modification of the technique reported by COLLIER et al., *Br. J. Pharmac.*, 32, 295–310 (1968). Physostigmine salicylate (b 1.0 mg/kg s.c.) produces 100% lethality when administered to mice grouped 10 per plastic cage (11×26×13 cm). Test agents were administered orally 30 minutes prior to physostigmine. The number of survivors were counted 20 minutes after physostigmine administration.

C. Antagonism of Acetic Acid Writhing. The acetic acid writhing test used was essentially that described by HENDERSHOT and FORSAITH, *J. Pharmac. Exp. Ther.*, 125, 237–240 (1959), except that acetic acid rather than phenylquinone was used to elicit writhing. Mice were injected with 0.6% aqueous acetic acid at 10 mg/kg i.p. 15 minutes after oral administration of the test drug. The number of writhes for each animal was counted during a 10 minute period starting 3 minutes after acetic acid treatment. A writhe was defined as a sequence of arching of the back, pelvic rotation and hind limb extension.

D. Antagonism of Electro-Convulsive Shock (ECS). For the ECS test, a modification of the method of TOMAN et al., *J. Neurophysiol.*, 9, 231–239 (1946), was used. One hour after oral administration of the test drug or vehicle, mice were administered a 13 mA, 60 cycle a.c. electroconvulsant shock (ECS) for 0.2 seconds via corneal electrodes. This shock intensity produces tonic convulsions, defined as extension of the hind limbs, in at least 95% of vehicle-treated mice.

Of the above test procedures for measuring CNS activity of antihistamines, the physostigmine-induced lethality test is believed to be a major index of non-sedating characteristics, since it reflects mainly central anticholinergic potency which is believed to contribute to sedative activity.

The results from the above test procedures are set forth in Table 2 below:

TABLE 2

	Antihistaminic Activity	CNS Activity		
	A. G. pig.	B. Physostigmine	C. Acetic	D. ECS
Com-pound	p.o. ED_{50} (mg/kg)	lethality ED_{50} (mg/kg)	writhing ED_{50} (mg/kg)	test ED_{50} (mg/kg)
A	0.15	320	147	160
B	.09	320	320	320

The above results demonstrate that the compounds of the invention are a potent antihistamines having low CNS activity indicative of non-sedation. Specifically, Compounds A and B are relatively inactive in all of the CNS test procedures, and in particular, they provide an ED_{50} in the physostigmine-induced lethality test of greater than 320.

Compound A was also tested to assess its sedative effects in another procedure:

Acute behavioral, neurologic and autonomic effects of Compound A were evaluated in mice by a modification of the method of Irwin [Irwin S., Drug Screening And Evaluation Of New Drugs In Animals, in *Animal And Clinical Pharmacologic Techniques in Drug Evaluation*, Nodine JM and Siegler PE (Eds)., Year Book Medical Publishers Inc., Chicago 1964, pp 36–54]. After oral administration of vehicle or drug, mice (CFI males, 20–24 g) were observed and manipulated to evaluate behavorial, neurologic and autonomic changes. A semi-quantitative scoring scale was used where signs normally present (e.g., spontaneous activity, alertness, pupil size) were assigned a "normal" score of 0 and scores of +1, +2 and +3 indicated slight, moderate and marked increases and scores of −1, −2 and −3 indicated slight, moderate and marked decreases from "normality". When a sign occurred that is not normally present (e.g., convulsions, tremors), its magnitude was graded on a 1–3 scale. Each treatment group consisted of 6 animals and evaluations were conducted 1 hour after dosing. Additional observations for lethality were made for up to 24 hours after dosing. Incidence is de-

fined as the observation occurring in an animal with a score of 2 or greater according to the scoring method defined above.

Effects of Compound A on behavior, neurologic function and automatic function in mice

Measurement	MED, mg/kg po*
Lethality	300
Reactivity	300
Decreased motor activity	300
Decreased muscle tone	300
Tremors/convulsions	300
Ataxia	300
Mydriasis	300
Ptosis	300

*Minimal effective dose, defined as the lowest dose that produced a score of 2 or greater according to Irwin (supra) in at least 3 of 6 animals tested at each dose.

From the above test results, it may be concluded that the compounds of the invention would be essentially non-sedating at a clinically useful antihistamic dosage. Compound B (i.e., the 8-fluoro compound) is particularly preferred because it has also shown very low toxicity.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptom being treated. A typical recommended dosage regimen is oral administration of from 5 to 100 mg/day, preferably 10 to 20 mg/day, in two to four divided doses to achieve relief of the symptoms.

The following examples are intended to illustrate, but not to limit, the present invention.

EXAMPLE I

A.

N-(1,1-Dimethylethyl)-3-methyl-2-pyridine carboxamide

2-cyano-3-methyl pyridine (400 g) is suspended in t-BuOH (800 mL) and the mixture heated to 70° C. Concentrated sulphuric acid (400 mL) is added dropwise over 45 minutes. The reaction is complete after a further 30 minutes at 75° C. The mixture is then diluted with water (400 mL), charged with toluene (600 mL) and brought to pH 10 with concentrated aqueous ammonia. The temperature is kept at 50°–55° C. during the work up. The toluene phase is separated, the aqueous layer reextracted and the combined toluene phases are washed with water. Removal of the toluene yields an oil, N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide, from which solid product may crystallize. Product yield of 97% is determined by internal standard assay on gas chromatograph.

B.

3-[2-(3-Fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide

Tetrahydrofuran (125 mL) and N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (1 equivalent) are charged and cooled to −40° C. under nitrogen. Two equivalents of n-butyllithium are then added over 40 minutes. When half the n-butyllithium is added the mixture turns purple. Sodium bromide (1.3 g) is added and then 3-fluoro-benzyl bromide (1.05 equivalents) is added dropwise (1:1 solution in tetrahydrofuran) over 40–50 minutes while the temperature is maintained at −40° C. After 30 minutes at −40° C., the mixture is diluted with water (250 mL) and the organic phase separated. This phase is dried over sodium sulphate and the solvent removed yielding an oil from which solid product, 3-[2-(3-fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide, may crystallize.

C.

3-[2-(3-Fluorophenyl)ethyl]-2-pyridine-carbonitrile

A solution of 3-[2-(3-fluorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (36.4 g, 0.121 mole) in 123 mL (202.3 g, 1.32 mole) of phosphorous oxychloride is heated at 110° C. for 3.5 hours and stirred at ambient temperature an additional 15 hours. The reaction is quenched with ice and water and the pH of the solution is brought to 8 by the addition of a saturated aqueous solution of potassium carbonate. The product is extracted into ethyl acetate and the solution is concentrated to a residue. Following purification by silica gel chromatography and trituration with pentane, 16.2 g (0.072 mole) of product is obtained in 60% yield.

D.

(1-Methyl-4-piperidinyl)[3-[2-(3-fluorophenyl)ethyl]-2-pyridinyl]methanone

To a solution of 3-[2-(3-fluorophenyl)ethyl]-2-pyridine carbonitrile (28.0 g, 0.123 mole) in 150 mL of dry THF is added 92 mL (1.48 moles/liter, 0.136 mole) of N-methylpiperidyl magnesium chloride over 10 minutes maintaining the temperature of 45°–50° C. The reaction is maintained at 40° C. to 50° C. for another 10 minutes and at ambient temperature for 45 minutes. The reaction is quenched to below pH 2 and aqueous hydrochloric acid and the resulting solution is stirred at 25° C. for 1 hour. The pH of the solution is adjusted to about 8, the product is extracted with ethylacetate, and the solution is concentrated to a residue. Following purification by silica gel chromatography, 38.3 g of product is obtained as a brown oil.

E.

8-Fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of (1-methyl-4-piperidinyl)[3-[2-(3-fluorophenyl)ethyl]-2-piperidinyl]methanone (15.0 g, 0.046 mole) in 74 mL (125.5 g, 0.837 mole) of trifluoromethanesulfonic acid is stirred at ambient temperature for 18 hours. The reaction is quenched with ice-water and the solution made basic with potassium hydroxide. The product is extracted into ethyl acetate. The ethyl acetate solution is filtered to remove insolubles and the filtrate is concentrated to a residue. Following purification by silica gel chromatography, 5.4 g (0.0175 mole) of product is obtained in 38% yield.

F.

8-Fluoro-11(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a stirred solution of 8-fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (10.5 g, 34 mmol) and triethylamine (5.2 g, 52 mmol) in dry toluene (120 mL) at 80° C. under an argon atmosphere, was added ethylchloroformate (18.5 g, 170 mmol) via a syringe. The reaction mixture was allowed to stir at this temperature for 30 minutes

and at room temperature for one hour. The reaction mixture was then filtered and solvent was removed. The residue was triturated with pentane to give 10.1 grams (yield=81%) of the title compound, m.p.=116°-118° C.

G.

8-Fluoro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo-[5,6]cyclohepta[1,2-b]pyridine

8-Fluoro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (3.6 g, 9.8 mmol.) was refluxed with KOH (4.5 g) in 50 mL of ethanol/water (1:1) for 66 hours under an argon atmosphere. The reaction mixture was poured into a brine solution and extracted twice with ethyl acetate. The extracts were combined and then dried over Na_2SO_4 and filtered. Solvent was removed to give 2.76 grams (yield=95%) of the title compound, m.p.=133.5°-134.5° C.

EXAMPLE II

A.

3-[2-(3-Fluorophenyl)ethenyl]-picolinamide

A solution of 2-cyano-3-picoline (142 g, 1.2 mole) and 3-fluorobenzaldehyde (164 g, 1.32 mole) in 750 mL of dry tetrahydrofuran (THF) is prepared. This solution is added dropwise to a solution of 162.0 grams of potassium t-butoxide (1.44 mole) dissolved in 750 mL of dry THF at −15° C. to −20° C.

The addition requires ½ hour, and the temperature is maintained below −15° C. The mixture is stirred at −15° to −20° C. for 1 hour, then at 0° to 5° C. for 2 hours.

Saturated NH_4Cl solution (400 mL) is added to the mixtured followed by 250 mL of H_2O. The mixture is stirred for ½ hour, and the aqueous layer is separated and extracted with 300 mL of CH_2Cl_2, which is combined with the THF layer. The organic solution is washed with 400 mL of saturated NH_4Cl solution, dried over Na_2SO_4, treated with charcol and filtered through diatomaceous earth.

The solvent is removed on a rotary evaporator, and the oily residue is dissolved in 350 mL of boiling toluene. The mixture is filtered hot to remove impurities and cooled overnight at 0° to 5° C. The off-white solid that precipitates is filtered, washed twice with 100 mL of cold toluene, and dried at 60° C. for 6 hours, yielding 122.1 grams (42.1%) of the title compound, m.p.=153°-155° C.

B.

3-[2-(3-Fluorophenyl)ethyl]-picolinamide

A solution is prepared by dissolving 121 grams of 3-[2-(3-fluorophenyl)ethenyl]-picolinamide (0.5 mole) in 500 mL of acetic acid. To the solution is added 8.0 grams of 5% Pd/C and the mixture is placed on a Parr hydrogenator overnight. A theoretical amount of H_2 is absorbed, and mixture is filtered through diatomaceous earth and poured into 4 liters of H_2O. The off-white suspension is stirred for 2 hours and cooled at 0° to 5° C. for 20 hours.

The solid product 3-[2-(3-fluorophenyl)ethyl]-picolinamide is filtered and washed three times with 100 mL of H_2O and dried at 60° C. for 20 hours, yielding 108 grams (yield=88.6%) of the title compound, m.p.=102°-104° C.

C.

3-[2-(3-Fluorophenyl)ethyl]-picolinic acid

A suspension of 73.2 grams of 3-[2-(3-fluorophenyl)ethyl]-picolinamide (0.3 mole) in 500 mL of ethanol and 125 grams of 45% KOH (1.0 mole) is prepared. H_2O (200 mL) is added, and the mixture is refluxed for 20 hours. TLC shows complete conversion to the acid.

The alcohol is removed by distillation until the vapor temperature reaches 100° C. The suspension is cooled to room temperature, 100 mL of H_2O is added and the solution is brought to a pH of 4–4.5 with 12N HCl (110 mL). The suspension is stirred for 1 hour and cooled overnight. The solid is filtered, washed three times with 100 mL of H_2O and dried at 65° C. for 24 hours, yielding 69.6 grams (yield=94.8%) of the title compound, m.p.=118°-122° C.

D.

8-Fluoro-6,11-dihydro-5H-benzo-[5,6]-cyclohepta[1,2-b]pyridin-11-one

A solution of 61.3 grams of 3-[2-(3-fluorophenyl)ethyl]-picolinic acid (0.25 mole) in 900 mL of tetrachloroethane is prepared. Anhydrous HCl gas is passed through the solution at room temperature for 1¼ hours. Oxalylchloride (48.3 grams, 0.38 mole) is carefully added, and stirred for 24–26 hours at room temperature (slight heating at 35°–40° C. for 4 hours is needed to obtain a dark solution). The solution is cooled to 0°–5° C., and 67 grams of $AlCl_3$ (0.5 mole) are slowly added over ½ hour. The mixture is stirred at 0° to 5° C. for 18 hours. An additional 17 grams of $AlCl_3$ (0.125 mole) is added, and mixture is stirred for 2 hours.

Then 500 mL of 3.7% HCl is added, and the mixture is stirred for ½ hour and filtered through diatomaceous earth. The top aqueous layer is separated, and the organic layer is washed twice with 500 mL of 3.7N HCl. The combined aqueous layer is washed twice with 500 mL of ether.

Benzene (1 liter) is added. The mixture is cooled to 5°–10° C. and brought to pH>9 with slow addition of 390 grams of 50% NaOH. The mixture is stirred for ½ hour and filtered through diatomaceous earth. The aqueous layer is separated and washed twice with 300 mL of benzene, which are combined with the first benzene layer.

The combined organic layers are washed with 250 mL of 5% $NaHCO_3$ and 250 mL of saturated NaCl solution. The organic layer is dried over Na_2SO_4, and solvent is removed leaving 49.6 grams of a yellow solid. The solid is dissolved in 100 mL of butyl acetate (hot) and cooled for 24–48 hours at 0° to 5° C. The solid is filtered, washed twice with 30 mL of cold ethyl acetate, and dried at 60° C. for 20 hours, yielding 38.8 grams (yield=68.5%) of the title compound, m.p.=116°-119° C.

E.

1-Methyl-4-[8-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl]piperidin-11-OL

A suspension is prepared by mixing 22.7 grams of 11-oxo-8-fluoro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (0.1 mole) with 500 mL of liquid NH_3, and 5.1 grams of Na(0.22 mole) are added. The resulting blue mixture is stirred for ½ hour. A solution containing 15.9 grams of 4-chloro-N-methyl-piperidine (0.12 mole)

in 400 mL of dry THF is slowly added over ½ hour and stirred for 2 hours at −25° C.

NH_4Cl (17.5 grams, 0.33 mole) is added, and the mixture is stirred for ½ hour until the mixture warms to 0° C. Saturated NH_4Cl solution (200 mL) is added, followed by 50 mL of H_2O, and mixture is stirred for ½ hour.

The aqueous layer is separated and extracted with 200 mL of CH_2Cl_2, which is combined with the THF layer. The combined organic layer is washed with 250 mL of saturated NH_4Cl solution, and dried over Na_2SO_4. The solvent is removed, leaving 34.7 grams of an oil, which crystallizes upon cooling.

The solid material is dissolved in 65 mL of hot n-butyl acetate and cooled overnight. The solid obtained is filtered, washed twice with 15 mL of cold ethyl acetate, and then dried at 75° C. for 6 hours, yielding 15.8 grams of the title compound, m.p.=123.5°-125° C.

The solvent is removed from the filtrate, leaving 11.0 grams of a yellow solid, which is dissolved in 20 mL boiling ethyl acetate, filtered hot, and cooled at 0°-5° C. for 4 hours. The solid obtained is filtered, washed twice with 5 mL of ethyl acetate, and dried at 60° C. for 5 hours, yielding 4.3 grams (total yield=61.7%).

F.

8-Fluoro-11-(1-methyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of 13.1 grams of 1-methyl-4-[8-fluoro-6,11-dihydro-11-hydroxy-5H-benzo-[5,6]cyclohepta[1,2-b]pyridin-11-yl]piperidine (0.04 mole) in 40 mL of 93% H_2SO_4 is prepared. The solution is stirred overnight at room temperature. CH_2Cl_2 (200 mL) is added, and with external cooling, the mixture is neutralized to pH>9 using 50% NaOH, while maintaining the temperature below 30° C. The aqueous layer is separated and re-extracted twice with 150 mL of CH_2Cl_2, which is combined with the first layer. The combined organic layer is washed with 150 mL of saturated $NaHCO_3$ solution and 150 mL of saturated NaCl solution, dried over Na_2SO_4, treated with charcoal and filtered through diatomaceous earth. The solvent is removed on a rotary evaporator leaving 12.9 grams of a yellow oil, which solidified upon standing.

The oil is dissolved in 70 mL of hot diisopropyl ether (6 parts) and poured into a hot solution of 9.5 grams of maleic acid (0.082 mole) dissolved in 60 mL of diisopropyl ether. The solution is cooled to 0°-5° C. with stirring and a yellow oil forms. The mixture is cooled overnight at 0°-5° C. with a yellow solid forming. The solid is filtered, washed twice with 20 mL of cold diisopropyl ether, and dried at 60° C. for 4 hours, yielding 18.2 grams.

This solid is dissolved in 2 parts boiling diisopropyl ether and filtered hot. The filtrate is cooled at 0°-5° C. with stirring for 1 hour with a heavy white precipitate forming. The suspension is cooled at 0°-5° C. for 6 hours. The solid formed is filtered, washed three times with 15 mL of cold diisopropyl ether and dried at 75°-80° C. for 48 hours, yielding 15.6 grams (yield=72.2%) of the title compound, m.p.=151°-152° C.

The product of step F above can then be employed in the process described in Example 1.F. and 1.G. to provide 8-fluoro-11-(1-ethoxycarbonyl-4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine and 8-fluoro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, respectively.

EXAMPLE III

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine acetic acid salt

To 12 grams of sodium hydroxide in 30 mL ethyl alcohol (70%) add 6 grams of 8-chloro-6,11-dihydro-11-(1-ethoxy-carbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (prepared as described in U.S. Pat. No. 4,282,233) and reflux with stirring for 24 hours. After about the first 6-8 hours an additional 30 mL of 70% ethyl alcohol may be added.

Remove about 50% of the solvent by distillation in vacuo. Add a small amount of ice water and acidify with glacial acetic acid.

Extract with chloroform (6-8×), since the product precipitates from the acetic acid solution as a thick emulsion which cannot be filtered.

Concentrate the chloroform extracts to a small volume and precipitate the product with hexane. Crude m.p. 197°-200° C.

Recrystallize from benzene-hexane to obtain the product, m.p. 199°-200° C. Yield 4.0-4.5 grams.

EXAMPLE IV

B.

3-[2-(3-Chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide

31.5 g of N-(1,1-dimethylethyl)-3-methyl-2-pyridine carboxamide (e.g., as prepared in step A of Example 1 above) is dissolved in 600 mL of dry tetrahydrofuran and the resulting solution is cooled to −40° C. Two equivalents of n-butyllithium in hexane are added while the temperature is maintained at −40° C. The solution turned deep purple-red. 1.6 g of sodium bromide is added and the mixture is stirred. A solution of 26.5 g (0.174 mole) m-chlorobenzylchloride in 125 mL of tetrahydrofuran is added while the temperature is maintained at −40° C. The reaction mixture is stirred until the reaction is complete as determined by thin layer chromatography. Water is added to the reaction until the color is dissipated. The reaction mixture is extracted with ethyl acetate, washed with water, and concentrated to a residue. A yield of 92% for the product is shown by chromatography.

C.

3-[2-(3-Chlorophenyl)ethyl]-2-pyridine-carbonitrile

A solution of 3-[2-(3-chlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (175 g, 0.554 mole), in 525 mL (863 g, 5.63 mole) of phosphorous oxychloride is heated at reflux for 3 hours. Completion of the reaction is determined by thin layer chromatography. Excess phosphorous oxychloride is removed by distillation at reduced pressure and the residue is quenched into a mixture of water and isopropanol. The pH is brought to 5-7 by addition of 50% aqueous sodium hydroxide solution while maintaining the temperature below 30° C. The crystalline slurry of crude product is filtered and washed with water. Crude product is purified by slurrying the wet cake in hot isopropanol followed by cooling at 0°-5° C. The product is filtered, washed with hexane and dried at below 50° C. Yield: 118 g (HPLC purity 95.7%), m.p. 72°-73° C., 89.4% of theory.

D.

(1-Methyl-4-piperidinyl)[3-[2-(3-chlorophenyl)ethyl]-2-pyridinyl]methanone hydrochloride

To a solution of product of Step C above (118 g, 0.487 mole) in 1.2 L of dry tetrahydrofuran is added 395 mL (2.48 mole/liter, 0.585 mole, 1.2 eq.) of N-methylpiperidyl magnesium chloride over about 15 minutes maintaining the temperature at 45° C.–50° C. by cooling with water as necessary. The reaction is maintained at 40° C. to 50° C. for about another 30 minutes. Completion of the reaction is determined by thin-layer chromatography. The reaction is quenched to pH below 2 with 2N hydrochloric acid and the resulting solution is stirred at about 25° C. for 1 hour. The bulk of the tetrahydrofuran is removed by distillation and the resulting solution is adjusted to pH 3.5 by the addition of aqueous sodium hydroxide. After cooling to 0° to 5° C., the crystalline hydrochloride salt product is filtered off, washed with ice cold water and dried to constant weight at 60° C. Yield: 168.2 g (HALC purity 94%), m.p. 183°–185° C., 89% of theory.

E.

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidylindene)5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a solution of a product of Step D above (59 g, 0.15 mole) in 120 mL (120 g, 6.0 mole) of hydrofluoric acid at −35° C. is added boron trifluoridine (44.3 g, 0.66 mole) over 1 hour. Completeness of the reaction is determined by thin-layer chromatography. The reaction is quenched using ice, water and potassium hydroxide to a final pH of 10. The product is extracted into toluene and the toluene solution is washed with water and brine. The toluene solution is concentrated to a residue, which is dissolved in hot hexane. Insolubles are removed by filtration and the filtrate is concentrated to an off-white powder. Yield: 45.7 g (HPLC purity: 96%), 92% of theory.

Alternative Step E

8-Chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

A solution of 177 g (0.49 mole) of a product of Step D above in 480 mL (814.1 g, 5.31 mole) of trifluoromethanesulfonic acid at 90°–95° C. for 18 hours under nitrogen. Completeness of the reaction is determined by thin-layer chromatography. The cooled reaction is quenched with ice-water and the pH is adjusted to 6 with barium carbonate. The product is extracted into methylene chloride, which is concentrated under reduced pressure to about 1 liter and washed with water. The product is extracted into 1N hydrochloric acid, which is treated with 30 g of Darco, and filtered through celite. The pH of the filtrate is adjusted to 10 with 50% aqueous sodium hydroxide and the product is extracted into methylene chloride, which is removed under reduced pressure. The residue is dissolved in hot hexane, which is filtered to remove insolubles. The filtrate is concentrated to a residual beige powder. Yield: 126 g (HPLC purity 80%), 65% of theory.

EXAMPLE V

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

The acetic acid salt prepared as in Example II is dissolved in a minimum amount of water and the solution is made basic with a dilute aqueous solution of potassium carbonate. A pink colored oil separates.

Extract the organic material with chloroform, wash with water and remove the solvent. Triturate the residue with hexane. Recrystallize from a large volume of hexane after charcoal decolorization to obtain the product, m.p. 151°–152° C.

EXAMPLE VI

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta [1,2-b]pyridine

A.

8-chloro-6,11-dihydro-11-(1-cyano-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

Dissolve 16.2 grams (0.05 mole) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidylidene)-5H-benzo[5,6-]cyclohepta[1,2-b]pyridine (prepared by the methods described in U.S. Pat. No. 3,326,924) in 300 mL of dry benzene. To this solution, add slowly under nitrogen a solution of cyanogen bromide (6.4 g) dissolved in 75 mL of benzene. Allow this mixture to stir at room temperature overnight (approximately 20 hours).

Filter the solution, and concentrate the filtrate in vacuo to a small volume and precipitate the product by the addition of petroleum ether or hexane until precipitation is complete. Filter and recrystallize from ethanol/water to yield the product 15 grams (89%), m.p. 140°–142° C.

Anal. Calcd. for $C_{20}H_{18}N_3Cl$: C,71.53; H,5.40; N,12.51. Found, C,71.73; H,5.43; N,12.27.

B.

8-Chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine.

A solution of 14 grams of the N-cyano compound from part A in 60 mL of concentrated hydrochloric acid, 600 mL of glacial acetic acid and 400 mL of water is refluxed with stirring for 20 hours. The solvents are removed in vacuo and the residue dissolved in water and neutralized with ammonium hydroxide. The material is extracted several times with chloroform, the chloroform extracts washed with water and concentrated to dryness, and the residue triturated with petroleum ether or hexane to yield 11.5 grams (93%) m.p. 149°–151° C. After recrystallization from hexane, the product melts at 150°–151° C.

Anal. Calcd. for $C_{19}H_{19}N_2Cl$: C,73.42; H,6.16; N,9.01. Found: C,73.19; H,6.14; N,8.91.

EXAMPLE VII

A.

N-(1,1-dimethylethyl)-3-[2-(4-fluorophenyl)ethyl]-2-pyridine carboxamide

To a cooled (−40° C.) solution of N-(1,1-dimethylethyl)-3-methyl-2-pyridinecarboxamide (38.4 g, 0.2 mole) in dry THF (250 mL) is added n-butyl lithium (185 mL, 0.44 mole). Then sodium bromide (1.9 g, 18 mmol.) is added and is allowed to stir for 15 minutes. 4-Fluorobenzylchloride (31.8 g. 0.22 mole) was added and the reaction is allowed to stir for 2½ hours while warming up to −5° C. The reaction is then quenched with water and the product is extracted twice with ethyl acetate followed by washing twice with brine. The organic phase is dried over Na_2SO_4, filtered and

solvent is removed to give desired compound (60.0 g) in 99% yield, m.p. 59°–61° C.

By a similar procedure, the corresponding 3-fluorophenyl, 3,4-dichlorophenyl, 3-bromophenyl, 4-chlorophenyl and 3,4-dibromophenyl analogs can be prepared by employing the appropriate substituted benzyl chloride.

B.

3-[2-(4-Fluorophenyl)ethyl]-2-pyridine-carbonitrile

The product of previous Step A (60.0 g, 0.2 mole) in $POCl_3$ (200 mL) is heated at 110° C. under an argon atmosphere for 3½ hours. The reaction mixture is poured onto ice and basified with 50% NaOH solution. It is then extracted three times with ethyl acetate, washed with water and brine, and dried over Na_2SO_4. Solvent is removed and the residue is passed through a coarse SiO_2 (60–200 mesh) column to give the desired product as a white solid (40 g) in 88% yield, m.p. 48°–49° C.

C.

9-Fluoro-5,6-dihydro-(1H)-benzo[5,6]cyclohepta[1,2-b]-pyridin-11-one

The product of Step B hereof (31.5 g, 139 mmol) is cyclized in polyphosphoric acid (1.24 kg) at 200° C. for 5½ hours. The hot reaction is poured into ice and then basified with 50% NaOH solution. The product is extracted three times with $CHCl_3$ and then washed with brine. The organic phase is dried (Na_2SO_4), filtered, and solvent is removed to give the desired product (20.4 g) in 64% yield, m.p. 78°–81° C. after recrystallization from diisopropyl ether.

D.

9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinyl)-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-OL

A solution of the product of previous Step C above (10.0 g, 44 mmol) in THF (100 mL) is added slowly to a cooled (−40° C.) solution of the Grignard reagent prepared from N-methyl-4-chloro-piperidine (57.9 mL, 88 mmol) in THF (70 mL). This is allowed to stir for about 1 hour while warming up to 0° C. The reaction is then quenched with NH_4Cl solution and then extracted twice with ethyl acetate. The organic phase is washed with brine, dried over Na_2SO_4, filtered and solvent removed. The residue is flash chromatographed and eluted with 5% methanol in $CHCl_3$ to give the desired compound (10.1 g) in 70% yield as white granular crystals, m.p. 126°–127° C. after recrystallization from diisopropyl ether.

E.

9-Fluoro-11-[1-methyl-4-piperidylene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To an ice-bath-cooled acid (146 mL) of H_2SO_4 and CF_3SO_3H (1:1) is added the product of previous Step D (7.3 g, 22.3 mmol). The reaction mixture is allowed to stir for ½ hour at ice bath temperature and then at room temperature for 1½ hour. The reaction mixture is poured onto ice and then basified with 50% NaOH solution. The product is extracted three times with ethyl acetate and washed with brine. The organic phase is desired (Na_2SO_4), filtered and solvent is removed to give a crude oil which is charcoaled and recrystallized from ethyl acetate and isopropyl ether to give the desired product (5.6 g) in 82% yield, m.p. 134.5°–135.5° C.

F.

9-fluoro-11-[1-ethoxycarbonyl-4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

To a stirred solution of the product of previous Step E (5.0 g, 16.2 mmol) and triethylamine (2.6 g, 26 mmol) in dry toluene (60 mL) at 80° C. under an argon atmosphere, is added ethylchloroformate (9.8 g, 90 mmol) via a syringe. The reaction is allowed to stir at this temperature for 30 minutes and at room temperature for an hour. The reaction is filtered and solvent is removed. The residue is passed through coarse SiO_2 (60–200 mesh), eluted with $CHCl_3$ to give the desired product (4.5 g) in 76% yield as a white solid, m.p. 112°–114° C. after trituration wih pentane.

G.

9-Fluoro-11-[4-piperidylidene]-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

The product of previous Step F (3.83 g, 10.4 mmol) is refluxed with KOH (4.6 g) in 50 mL of ethanol/H_2O (1:1) for 4 hours under an argon atmosphere. The reaction mixture is poured into a brine solution and extracted twice with ethyl acetate. It is then dried over Na_2SO_4 and filtered. Solvent is removed to give the named compound (2.86 g) in 90% yield, m.p. 138°–140° C.

EXAMPLE VIII

A.

3-[2-(3,4-Dichlorophenyl)ethyl]-2-pyridinecarbonitrile

A solution of 3-[2-(3,4-dichlorophenyl)ethyl]-N-(1,1-dimethylethyl)-2-pyridine carboxamide (37.8 g, 0.107 mole) in 120 mL (197.4 g, 1.29 mole) of phosphorous oxychloride is heated at 110° C. for 4.5 hours. Completion of the reaction is determined by thin-layer chromotography. The reaction is quenched with ice and H_2O and the pH of the solution is brought to 8 by the addition of a saturated solution of potassium carbonate. The product is extracted into ethylacetate. The solution is concentrated to a solid residue which upon recrystallization from diethyl ether/ethyl acetate provides the desired product, (27.1 g, 0.098 mole), in 91.6% yield.

B.

(1-Methyl-4-piperidinyl)-[3-[2-(3,4-dichlorophenyl)ethyl]-2-piperidinyl]methanone

To a solution of the product of previous Step A (21.2 g, 0.0765 mole) in 140 mL of dry tetrahydrofuran at reflux is added 50 mL (1.48 mole/liter, 0.074 mole) of N-methylpiperidyl magnesium chloride over about 10 minutes. The reaction is maintained at reflux for an additional 10 minutes. The reaction is quenched to pH below 2 with aqueous hydrochloric acid and the resulting solution is stirred at 25° C. for 1 hour. The pH of the solution is adjusted to about 8, the product is extracted with ethyl acetate and the solution is concentrated to a residue. Following purification by silica gel chromatography and crystallization from diisopropyl ether, the desired product (19.86 g, 0.0526 mole) is obtained in 69% yield.

C.

8,9-Dichloro-6,11-dihydro-11-(1-methyl-4-piperidylidene-5H-benzo[5,6]-cyclohepta[1,3-b[pyridine

A solution of the product of previous Step B (9.8 g, 0.0259 mole) in 100 mL (169.6 g, 1.13 mole) of trifluoromethanesulfonic acid is heated at 85° C. for 48 hours. The reaction is quenched with ice-water and the solution made basic with potassium hydroxide. The product is extracted into ethyl acetate and the solution is concentrated to a residue. Following purification by reverse phase HPLC and crystallization from acetone/-pentane, the desired product (2.38 g, 0.0066 mole) is obtained in 25.5% yield.

D.

8,9-Dichloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

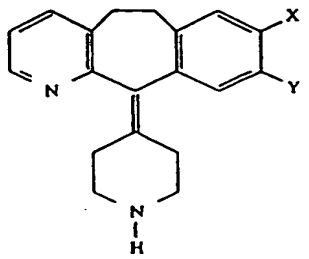
Ethyl chloroformate (1.9 mL, 2.16 g; 0.020 mole) in 10 mL of toluene is slowly added at 80° C. to a solution of the product of previous Step C (1.44 g, 0.004 mole) and triethylamine (1.5 mL, 1.09 g, 0.011 mole) in 50 mL of toluene. Following complete addition, the temperature is maintained at 80° C. for 2.5 hours. Insolubles in the reaction mixture are removed by filtration, and the filtrate is concentrated to a residue. Following silica gel chromotography and crystallization from pentane, the desired product (1.2 g, 0.0029 mole) is obtained in 72.5% yield.

E.

8,9-Dichloro-11-(4-piperidylidene)-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine

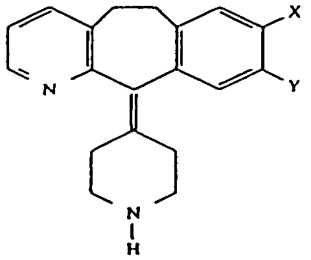
A solution of the product of previous Step D (0.925 g, 0.0022 mole) and potassium hydroxide (1.5 g, 0.039 mole) in 7.5 mL of water and 8.5 mL of ethanol is heated at reflux for 27 hours. The reaction mixture is diluted with water and the product is extracted into ethyl acetate. The solution is concentrated to a residue and the named compound (0.685 g, 0.0020 mole) is obtained from crystallization with toluene. Yield 91%.

By employing the appropriately substituted benzyl chloride in Example I. B. above in place of 3-fluorobenzyl chloride, the following compounds of formula I or their pharmaceutically acceptable salts may also be prepared:



Compound No.	X	Y
1	H	Cl
2	H	Br
3	H	I
4	H	CF_3
5	Br	H

-continued



Compound No.	X	Y
6	I	H
7	CF_3	H
8	F	F
9	Br	Br
10	Cl	F
11	Cl	Br
12	F	Cl
13	Br	Cl
14	F	Br
15	Br	F

The following formulations exemplify some of the dosage forms of the compositions of this invention. In each, the term "active compound" designates a compound of the invention, e.g., Compound A or Compound B, or a pharmaceutically acceptable salt or solvate thereof.

PHARMACEUTICAL DOSAGE FORM EXAMPLES

EXAMPLE A

		Tablets	
No.	Ingredient	mg/tablet	mg/tablet
1.	Active Compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix item nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with item no. 3. Mill the damp granules through a coarse screen (e.g., ¼") if needed. Dry the damp granules. Screen the dried granules if needed and mix with item no. 4 and mix for 10–15 minutes. Add item no. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B

		Capsules	
No.	Ingredient	mg/capsule	mg/capsule
1.	Active Compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade,	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

Method of Manufacture

Mix item nos. 1, 2 and 3 in a suitable blender for 10–15 minutes. Add item no. 4 and mix for 1–3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

EXAMPLE C

Ingredient	Parenteral mg/vial	mg/vial
Active Compound Sterile Powder	100	500

Add sterile water for injection or bacteriostatic water for injection, for reconstitution.

EXAMPLE D

Ingredient	Injectable mg/vial
Active Compound	100
Methyl para-hydroxybenzoate	1.8
Propyl para-hydroxybenzoate	0.2
Sodium Bisulfite	3.2
Disodium Edetate	0.1
Sodium Sulfate	2.6
Water for Injection q.s. ad	1.0 mL

Method of Manufacture

1. Dissolve the para-hydroxybenzoates in a portion (85% of the final volume) of the water for injection at 65°–70° C.
2. Cool to 25°–35° C. Charge and dissolve the sodium bisulfite, disodium edetate and sodium sulfate.
3. Charge and dissolve active compound.
4. Bring the solution to final volume by adding water for injection.
5. Filter the solution through a 0.22 membrane and fill into appropriate containers.
6. Finally, sterilize the units by autoclaving.

The following examples illustrate formulations including a compound of formula I for transdermal application. Compound A refers to 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, but again other compounds of formula I such as compound B above may be employed in its place.

EXAMPLE E

Ointment	mg/g
Compound A	200
White Petrolatum	800

EXAMPLE F

Ointment	mg/g
Compound A	200
Propylene glycol	200
White Petrolatum	600

EXAMPLE G

Cream	mg/g
Compound A	200
Mineral Oil	48
White Petrolatum	120
Cetostearyl Alcohol	57.6
Polyethylene glycol 1000 monocetylether	18.0
Propylene glycol	80
Water	476.4

EXAMPLE H

Gel	mg/g
Compound A	200
Pluronic F-127	250
Ethanol	200
Water	350

EXAMPLE I

Cream	mg/g
Compound A	100.00
Mineral Oil	54.0
White Petrolatum	135.0
Cetostearyl Alcohol	65.0
Ceteth 20	20.0
Propylene Glycol	100.0
Water q.s. ad	1.0 g

The formulations of Examples E–I above can be packaged to produce a "reservoir type" transdermal patch with or without a rate-limiting patch membrane. The size of the patch and or the rate limiting membrane can be chosen to deliver the transdermal flux rates desired. Such a transdermal patch can consist of a polypropylene or polyester impervious backing member heat sealed to a polypropylene porous/permeable membrane to from a reservior therebetween. The patch can include a pharmaceutically acceptable adhesive (such as a acrylate adhesive) on the membrane layer to adhere the patch to the skin of the host, e.g., a mammal such as a human. A release liner such as a polyester release liner can also be provided to cover the adhesive layer prior to application of the patch to the skin as is conventional in the art. This patch assembly can be packaged in an aluminum foil or other suitable pouch again as is conventional in the art.

Alternatively, a compound of formula I or a salt thereof can be formulated into a "matrix-type" transdermal patch as in Examples J and K below. Drug Delivery Systems Characteristics and Biomedical Application, R. L Juliano, ed., Oxford University Press. N.Y. (1980); and Controlled Drug Delivery Vol. I Basic Concepts, Stephen D. Bruck (1983) described the theory and application of methods useful for transdermal delivery systems. The relevant teachings of these texts are herein incorporated by reference. The drug-matrix could be formed utilizing various polymers, e.g. silicone, polyvinyl alcohol, polyvinyl chloride-vinyl acetate copolymer. The "drug matrix" may then be packaged into an appropriate transdermal patch.

EXAMPLE J

Patch	mg/g
Compound A	200
silicone polymer	800

EXAMPLE K

Patch	mg/g
Compound A	300
Polyvinyl chloride vinyl acetate co-polymer	700

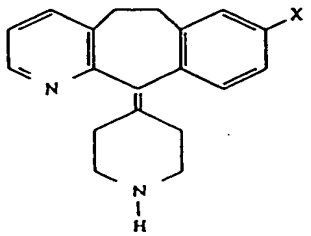
The invention also contemplates a package which contains a specific number of transdermal patches that may be utilized to complete a specified course of treatment. For example a package containing 7, 24 hour patches would be utilized to complete a one week course of therapy.

The relevant teachings of all published references cited herein as incorporated by reference.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

We claim:

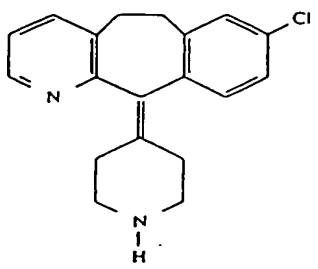
1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein X represents Cl or F.

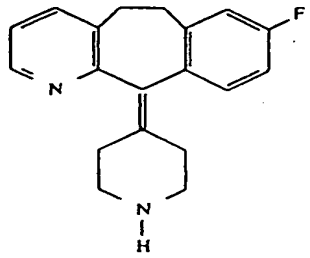
2. A compound defined in claim 1 in the form of the acetic acid salt.

3. A compound having the structural formula



or a pharmaceutically acceptable salt thereof.

4. A compound having the structural formula



or a pharmaceutically acceptable salt thereof.

5. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of a compound as defined in claim 1 in combination with a pharmaceutically acceptable carrier.

6. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 2 in combination with a pharmaceutically acceptable carrier.

7. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 3 in combination with a pharamaceutically acceptable carrier.

8. An antihistaminic pharmaceutical composition which comprises an antihistaminic effective amount of the compound defined in claim 4 in combination with a pharmaceutically acceptable carrier.

9. A composition as defined in claim 7 in unit dosage form.

10. A composition as defined in claim 8 in unit dosage form.

11. A transdermally acceptable pharmaceutical composition comprising an anti-allergic effective amount of a compound as defined in claim 1 and a pharamaceutically acceptable transdermal carrier.

12. A transdermally acceptable pharamaceutical composition comprising a anti-allergic effective amount of a compound as defined in claim 3 and a pharmaceutically acceptable transdermal carrier.

13. A transdermally acceptable pharmaceutical composition comprising an anti-allergic effective amount of a compound as defined in claim 4 and a pharmaceutically acceptable transdermal carrier.

14. A method for treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 1.

15. A method of treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 3.

16. A method for treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of a compound as defined in claim 4.

* * * * *

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The most severe reactions usually involve the cardiovascular system, causing severe hypotension and vasomotor collapse. IV fluids should be started and the patient should be recumbent with legs elevated. Epinephrine (1:100,000) should be given slowly IV (5 to 10 μg/min) with close observation for development of side effects, including headache, tremulousness, nausea, and arrhythmias. The underlying severe hypotension may be due to vasodilation, hypovolemia from loss of fluid, myocardial insufficiency (rarely), or a combination of these. Each has a specific treatment, and often the treatment of one exacerbates the others. The appropriate therapy may be clarified if central venous pressure **(CVP)** and left atrial pressure can be obtained (see also in Ch. 23). A low CVP and normal left atrial pressure indicate peripheral vasodilation and/or hypovolemia. Vasodilation should respond to the epinephrine (which will also retard the loss of intravascular fluid).

Hypovolemia is usually the major cause of the hypotension. The CVP and left atrial pressure are both low, and large volumes of saline must be given, with BP monitored until the CVP rises to normal. Colloid plasma expanders (eg, dextran) are rarely necessary. Only if fluid replacement does not restore normal BP should one initiate treatment *cautiously* with vasopressor drugs (eg, metaraminol).

In the rare instance of myocardial insufficiency, both CVP and left atrial pressure will be elevated. Isoproterenol 1 mg diluted in 500 mL of 5% dextrose is infused at 0.5 to 1 mL/min. *The patient should be monitored carefully, for the isoproterenol may cause cardiac arrhythmias and hypotension due to peripheral vasodilation.*

Cardiac arrest may occur, requiring immediate resuscitation (see CARDIAC ARREST AND CARDIOPULMONARY RESUSCITATION in Ch. 25). Further therapy depends on ECG findings.

When all the above measures have been instituted, diphenhydramine (50 to 75 mg IV slowly over 3 min) and glucocorticoids may then be given for treatment of slow-onset urticaria, asthma, laryngeal edema, or hypotension. Methylprednisolone 40 mg IV (or equivalent) should be given and repeated if necessary 8 h later. Complications (eg, MI, cerebral edema) should be watched for and treated specifically. Patients with severe reactions should remain in a hospital under observation for 24 h after recovery to ensure adequate treatment in case of relapse.

Anyone who has had an anaphylactic reaction to a stinging insect should be provided with a kit containing a pre-filled syringe of epinephrine and an epinephrine nebulizer (the latter is for topical therapy of upper airways angioedema) to allow prompt self-treatment of any future reaction. Such a person should also be evaluated for venom immunotherapy (desensitization).

DISORDERS OF VASOACTIVE MEDIATORS

Disorders having manifestations of vasoactive mediators derived from mast cells and other sources (even though an IgE-mediated or other immunologic mechanism may not be involved).

Urticaria; Angioedema

(Hives; Giant Urticaria; Angioneurotic Edema)

Urticaria: *Local wheals and erythema in the dermis.* **Angioedema:** *An eruption similar to urticaria, but with larger edematous areas that involve both dermis and subcutaneous structures.*

Etiology

Acute urticaria and angioedema are essentially anaphylaxis limited to the skin and subcutaneous tissues and can be due to drug allergy, insect stings or bites, desensitization injections, or ingestion of certain foods (particularly eggs, shellfish, nuts, or fruits). Some

reactions occur exp..sively following ingestion of minute a...ounts. Others (eg, reactions to strawberries) may occur only after overindulgence, and possibly result from direct (toxic) mediator liberation. Urticaria may accompany or even be the first symptom of several viral infections, including hepatitis, infectious mononucleosis, and rubella. Some acute reactions are unexplained, even when recurrent. If acute angioedema is recurrent, progressive, and never associated with urticaria, a hereditary enzyme deficiency should be suspected (see HEREDITARY ANGIOEDEMA, below).

Chronic urticaria and angioedema lasting > 3 wk are more difficult to explain, and only in exceptional cases can a specific cause be found. The reactions are rarely IgE-mediated. Occasionally, chronic ingestion of an unsuspected drug or chemical is responsible; eg, from penicillin in milk; from the use of nonprescription drugs; or from preservatives, dyes, or other food additives. Chronic underlying disease (SLE, polycythemia vera, lymphoma, or infection) should be ruled out. Though often suspected, controllable psychogenic factors are rarely identified. Urticaria caused by physical agents is discussed in PHYSICAL ALLERGY, below. A few patients with intractable urticaria are hyperthyroid. Occasionally, urticaria may be the first or only visible sign of cutaneous vasculitis.

Symptoms and Signs

In **urticaria**, pruritus (generally the first symptom) is followed shortly by the appearance of wheals that may remain small (1 to 5 mm) or may enlarge. The larger ones tend to clear in the center and may be noticed first as large rings (> 20 cm across) of erythema and edema. Ordinarily, crops of hives come and go; a lesion may remain in one site for several hours, then disappear, only to reappear elsewhere. If a lesion persists ≥ 24 h, one should think of the possibility of vasculitis. **Angioedema** is *a more diffuse swelling of loose subcutaneous tissue:* dorsum of hands or feet, eyelids, lips, genitalia, mucous membranes. Edema of the upper airways may produce respiratory distress, and the stridor may be mistaken for asthma.

Diagnosis

The cause of acute urticaria is usually obvious. Even when it is not, a diagnostic investigation is seldom required because of the self-limited, nonrecurrent nature of these reactions. In chronic urticaria, an underlying chronic disease should be ruled out by a careful history and physical examination and routine screening tests. Eosinophilia is uncommon in urticaria. Other tests (eg, stool examination for ova and parasites, serum complement, antinuclear Ab, and sinus or dental x-rays) are not usually worthwhile without additional clinical indications.

Treatment

Acute urticaria is a self-limited condition that generally subsides in 1 to 7 days; hence, treatment is chiefly palliative. If the cause is not obvious, all nonessential drugs should be stopped until the reaction has subsided. Symptoms usually can be relieved with an oral antihistamine (eg, diphenhydramine 50 to 100 mg q 4 h, hydroxyzine 25 to 100 mg bid, or cyproheptadine 4 to 8 mg q 4 h). A glucocorticoid (eg, prednisone 30 to 40 mg/day orally) may be necessary for the more severe reactions, particularly when associated with angioedema. Topical glucocorticoids are of no value. Epinephrine 1:1000, 0.3 mL s.c., should be the first treatment for **acute pharyngeal or laryngeal angioedema.** This may be supplemented with topical treatment; eg, nebulized epinephrine 1:100, and an IV antihistamine (eg, diphenhydramine 50 to 100 mg). This usually prevents airways obstruction, but one must be prepared to intubate or perform a tracheostomy and give O_2.

In **chronic urticaria**, spontaneous remissions occur within 2 yr in about ½ of cases. Control of stress often helps reduce the frequency and severity of episodes. Certain drugs (eg, aspirin) may aggravate symptoms, as will alcoholic beverages, coffee, and tobacco smoking; if so, they should be avoided. When urticaria is produced by aspirin, sensitivity to related NSAIDs and to the food- and drug-coloring additive tartrazine should be investigated (see also PERENNIAL RHINITIS, above). Oral antihistamines with a tranquilizing

effect are usually beneficial (eg, hydroxyzine 25 to 50 mg tid or cyproheptadine 4 to 8 mg q 4 to 8 h for adults; for children hydroxyzine 2 mg/kg/day divided q 6 h, and cyproheptadine 0.25 to 0.5 mg/kg/day divided q 6 to 8 h). Doxepin 25 to 50 mg bid may be the most effective agent for some adult patients. All reasonable measures should be used before resorting to glucocorticoids, which are frequently effective but, once started, may have to be continued indefinitely.

Hereditary Angioedema

A form of angioedema transmitted as an autosomal dominant trait and associated with a deficiency of serum inhibitor of the activated first component of complement. In 85% of cases, the deficiency is due to a lack of the C1 esterase inhibitor **(C1 INH)**; in 15%, to C1 INH malfunction. A positive family history is the rule, but there are exceptions. The edema is typically unifocal, indurated, painful rather than pruritic, and unaccompanied by urticaria. Attacks are often precipitated by trauma or viral illness, and are aggravated by emotional stress. The GI tract is often involved, with nausea, vomiting, colic, and even signs of intestinal obstruction. The condition may cause fatal upper airways obstruction. **Diagnosis** may be made by measuring C4, which is low even between attacks, or more specifically by showing C1 INH deficiency by immunoassay, and by a functional assay if the former is unexpectedly normal.

Treatment

The edema progresses until complement components have been consumed. Acute attacks that threaten to produce airways obstruction therefore should be treated promptly by establishing an airway. ϵ-Aminocaproic acid 8 gm q 4 h may succeed in ending the attack. The use of fresh frozen plasma is controversial. Epinephrine, an antihistamine, and a glucocorticoid should be given, but there is no proof that these drugs are effective.

For short-term prophylaxis of the previously untreated patient (as before a dental procedure, endoscopy, or surgery) 2 u. of fresh frozen plasma can be given. Although theoretically a complement substrate in the plasma might provoke an attack, this has not been observed in symptom-free patients. Recently, a partially purified C1 INH fraction of pooled plasma has been shown to be safe and effective for prophylaxis, but it is unavailable for general use. If time permits, it is preferable to treat the patient for 3 to 5 days with an androgen (see below).

For long-term prophylaxis, androgens are effective. One of the impeded androgens should be used. Treatment is begun with oral stanozolol 2 mg tid or danazol 200 mg tid. Stanozolol is less expensive. Once control is achieved, the dosage should be reduced as much as possible to reduce the cost and, in women, to minimize masculinizing side effects. These drugs not only are effective but also have been shown to raise the low C1 INH and C4 toward normal.

Mastocytosis

A condition of unknown etiology characterized by an excessive accumulation of mast cells in various body organs and tissues. Normally, tissue mast cells contribute to host defense by releasing potent preformed mediators (eg, histamine) from their granules and by generating newly formed mediators (eg, leukotrienes) from membrane lipids. Normal tissue mast cells also mediate the symptoms of common allergic reactions by means of IgE Abs attached to specific surface receptors.

Mastocytosis can occur in 3 forms: **mastocytoma** (*a benign cutaneous tumor*); **urticaria pigmentosa** (*multiple small cutaneous collections of mast cells that develop as salmon-colored or brown macules and papules*, which urticate when stroked and may become vesicular or even bullous); and **systemic mastocytosis** (*mast cell infiltrates in the skin, lymph nodes, liver, spleen, GI tract, and bones*).

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The most severe reactions usually involve the cardiovascular system, causing severe hypotension and vasomotor collapse. IV fluids should be started and the patient should be recumbent with legs elevated. Epinephrine (1:100,000) should be given slowly IV (5 to 10 μg/min) with close observation for development of side effects, including headache, tremulousness, nausea, and arrhythmias. The underlying severe hypotension may be due to vasodilation, hypovolemia from loss of fluid, myocardial insufficiency (rarely), or a combination of these. Each has a specific treatment, and often the treatment of one exacerbates the others. The appropriate therapy may be clarified if central venous pressure **(CVP)** and left atrial pressure can be obtained (see also in Ch. 23). A low CVP and normal left atrial pressure indicate peripheral vasodilation and/or hypovolemia. Vasodilation should respond to the epinephrine (which will also retard the loss of intravascular fluid).

Hypovolemia is usually the major cause of the hypotension. The CVP and left atrial pressure are both low, and large volumes of saline must be given, with BP monitored until the CVP rises to normal. Colloid plasma expanders (eg, dextran) are rarely necessary. Only if fluid replacement does not restore normal BP should one initiate treatment *cautiously* with vasopressor drugs (eg, metaraminol).

In the rare instance of myocardial insufficiency, both CVP and left atrial pressure will be elevated. Isoproterenol 1 mg diluted in 500 mL of 5% dextrose is infused at 0.5 to 1 mL/min. *The patient should be monitored carefully, for the isoproterenol may cause cardiac arrhythmias and hypotension due to peripheral vasodilation.*

Cardiac arrest may occur, requiring immediate resuscitation (see CARDIAC ARREST AND CARDIOPULMONARY RESUSCITATION in Ch. 25). Further therapy depends on ECG findings.

When all the above measures have been instituted, diphenhydramine (50 to 75 mg IV slowly over 3 min) and glucocorticoids may then be given for treatment of slow-onset urticaria, asthma, laryngeal edema, or hypotension. Methylprednisolone 40 mg IV (or equivalent) should be given and repeated if necessary 8 h later. Complications (eg, MI, cerebral edema) should be watched for and treated specifically. Patients with severe reactions should remain in a hospital under observation for 24 h after recovery to ensure adequate treatment in case of relapse.

Anyone who has had an anaphylactic reaction to a stinging insect should be provided with a kit containing a pre-filled syringe of epinephrine and an epinephrine nebulizer (the latter is for topical therapy of upper airways angioedema) to allow prompt self-treatment of any future reaction. Such a person should also be evaluated for venom immunotherapy (desensitization).

DISORDERS OF VASOACTIVE MEDIATORS

Disorders having manifestations of vasoactive mediators derived from mast cells and other sources (even though an IgE-mediated or other immunologic mechanism may not be involved).

Urticaria; Angioedema

(Hives; Giant Urticaria; Angioneurotic Edema)

Urticaria: *Local wheals and erythema in the dermis.* **Angioedema:** *An eruption similar to urticaria, but with larger edematous areas that involve both dermis and subcutaneous structures.*

Etiology

Acute urticaria and angioedema are essentially anaphylaxis limited to the skin and subcutaneous tissues and can be due to drug allergy, insect stings or bites, desensitization injections, or ingestion of certain foods (particularly eggs, shellfish, nuts, or fruits). Some

reactions occur exp...sively following ingestion of minute a...ounts. Others (eg, reactions to strawberries) may occur only after overindulgence, and possibly result from direct (toxic) mediator liberation. Urticaria may accompany or even be the first symptom of several viral infections, including hepatitis, infectious mononucleosis, and rubella. Some acute reactions are unexplained, even when recurrent. If acute angioedema is recurrent, progressive, and never associated with urticaria, a hereditary enzyme deficiency should be suspected (see HEREDITARY ANGIOEDEMA, below).

Chronic urticaria and angioedema lasting > 3 wk are more difficult to explain, and only in exceptional cases can a specific cause be found. The reactions are rarely IgE-mediated. Occasionally, chronic ingestion of an unsuspected drug or chemical is responsible; eg, from penicillin in milk; from the use of nonprescription drugs; or from preservatives, dyes, or other food additives. Chronic underlying disease (SLE, polycythemia vera, lymphoma, or infection) should be ruled out. Though often suspected, controllable psychogenic factors are rarely identified. Urticaria caused by physical agents is discussed in PHYSICAL ALLERGY, below. A few patients with intractable urticaria are hyperthyroid. Occasionally, urticaria may be the first or only visible sign of cutaneous vasculitis.

Symptoms and Signs

In **urticaria**, pruritus (generally the first symptom) is followed shortly by the appearance of wheals that may remain small (1 to 5 mm) or may enlarge. The larger ones tend to clear in the center and may be noticed first as large rings (> 20 cm across) of erythema and edema. Ordinarily, crops of hives come and go; a lesion may remain in one site for several hours, then disappear, only to reappear elsewhere. If a lesion persists ≥ 24 h, one should think of the possibility of vasculitis. **Angioedema** is *a more diffuse swelling of loose subcutaneous tissue:* dorsum of hands or feet, eyelids, lips, genitalia, mucous membranes. Edema of the upper airways may produce respiratory distress, and the stridor may be mistaken for asthma.

Diagnosis

The cause of acute urticaria is usually obvious. Even when it is not, a diagnostic investigation is seldom required because of the self-limited, nonrecurrent nature of these reactions. In chronic urticaria, an underlying chronic disease should be ruled out by a careful history and physical examination and routine screening tests. Eosinophilia is uncommon in urticaria. Other tests (eg, stool examination for ova and parasites, serum complement, antinuclear Ab, and sinus or dental x-rays) are not usually worthwhile without additional clinical indications.

Treatment

Acute urticaria is a self-limited condition that generally subsides in 1 to 7 days; hence, treatment is chiefly palliative. If the cause is not obvious, all nonessential drugs should be stopped until the reaction has subsided. Symptoms usually can be relieved with an oral antihistamine (eg, diphenhydramine 50 to 100 mg q 4 h, hydroxyzine 25 to 100 mg bid, or cyproheptadine 4 to 8 mg q 4 h). A glucocorticoid (eg, prednisone 30 to 40 mg/day orally) may be necessary for the more severe reactions, particularly when associated with angioedema. Topical glucocorticoids are of no value. Epinephrine 1:1000, 0.3 mL s.c., should be the first treatment for **acute pharyngeal or laryngeal angioedema**. This may be supplemented with topical treatment; eg, nebulized epinephrine 1:100, and an IV antihistamine (eg, diphenhydramine 50 to 100 mg). This usually prevents airways obstruction, but one must be prepared to intubate or perform a tracheostomy and give O_2.

In **chronic urticaria**, spontaneous remissions occur within 2 yr in about ½ of cases. Control of stress often helps reduce the frequency and severity of episodes. Certain drugs (eg, aspirin) may aggravate symptoms, as will alcoholic beverages, coffee, and tobacco smoking; if so, they should be avoided. When urticaria is produced by aspirin, sensitivity to related NSAIDs and to the food- and drug-coloring additive tartrazine should be investigated (see also PERENNIAL RHINITIS, above). Oral antihistamines with a tranquilizing

effect are usually beneficial (eg, hydroxyzine 25 to 50 mg tid or cyproheptadine 4 to 8 mg q 4 to 8 h for adults; for children hydroxyzine 2 mg/kg/day divided q 6 h, and cyproheptadine 0.25 to 0.5 mg/kg/day divided q 6 to 8 h). Doxepin 25 to 50 mg bid may be the most effective agent for some adult patients. All reasonable measures should be used before resorting to glucocorticoids, which are frequently effective but, once started, may have to be continued indefinitely.

Hereditary Angioedema

A form of angioedema transmitted as an autosomal dominant trait and associated with a deficiency of serum inhibitor of the activated first component of complement. In 85% of cases, the deficiency is due to a lack of the C1 esterase inhibitor (**C1 INH**); in 15%, to C1 INH malfunction. A positive family history is the rule, but there are exceptions. The edema is typically unifocal, indurated, painful rather than pruritic, and unaccompanied by urticaria. Attacks are often precipitated by trauma or viral illness, and are aggravated by emotional stress. The GI tract is often involved, with nausea, vomiting, colic, and even signs of intestinal obstruction. The condition may cause fatal upper airways obstruction. **Diagnosis** may be made by measuring C4, which is low even between attacks, or more specifically by showing C1 INH deficiency by immunoassay, and by a functional assay if the former is unexpectedly normal.

Treatment

The edema progresses until complement components have been consumed. Acute attacks that threaten to produce airways obstruction therefore should be treated promptly by establishing an airway. ϵ-Aminocaproic acid 8 gm q 4 h may succeed in ending the attack. The use of fresh frozen plasma is controversial. Epinephrine, an antihistamine, and a glucocorticoid should be given, but there is no proof that these drugs are effective.

For short-term prophylaxis of the previously untreated patient (as before a dental procedure, endoscopy, or surgery) 2 u. of fresh frozen plasma can be given. Although theoretically a complement substrate in the plasma might provoke an attack, this has not been observed in symptom-free patients. Recently, a partially purified C1 INH fraction of pooled plasma has been shown to be safe and effective for prophylaxis, but it is unavailable for general use. If time permits, it is preferable to treat the patient for 3 to 5 days with an androgen (see below).

For long-term prophylaxis, androgens are effective. One of the impeded androgens should be used. Treatment is begun with oral stanozolol 2 mg tid or danazol 200 mg tid. Stanozolol is less expensive. Once control is achieved, the dosage should be reduced as much as possible to reduce the cost and, in women, to minimize masculinizing side effects. These drugs not only are effective but also have been shown to raise the low C1 INH and C4 toward normal.

Mastocytosis

A condition of unknown etiology characterized by an excessive accumulation of mast cells in various body organs and tissues. Normally, tissue mast cells contribute to host defense by releasing potent preformed mediators (eg, histamine) from their granules and by generating newly formed mediators (eg, leukotrienes) from membrane lipids. Normal tissue mast cells also mediate the symptoms of common allergic reactions by means of IgE Abs attached to specific surface receptors.

Mastocytosis can occur in 3 forms: **mastocytoma** (*a benign cutaneous tumor*); **urticaria pigmentosa** (*multiple small cutaneous collections of mast cells that develop as salmon-colored or brown macules and papules*, which urticate when stroked and may become vesicular or even bullous); and **systemic mastocytosis** (*mast cell infiltrates in the skin, lymph nodes, liver, spleen, GI tract, and bones*).

ticular, histamine-induced bronchospasm may involve an additional, reflex component that arises from irritation of afferent vagal nerve endings (*see* Eyre and Chand, in Ganellin and Parsons, 1982; Nadel and Barnes, 1984).

The uterus of some species contracts to histamine; in the human uterus, gravid or not, the response is negligible. Responses of intestinal muscle also vary with species and region, but the classical effect is contraction. Bladder, ureter, gallbladder, iris, and many other smooth muscle preparations are affected little or inconsistently by histamine.

Exocrine Glands. As mentioned above, histamine is an important physiological regulator of gastric acid secretion. This effect is mediated by H_2 receptors (*see* Chapter 37).

Nerve Endings: Pain, Itch, and Indirect Effects. Histamine stimulates various nerve endings. Thus, when released in the epidermis, it causes itch; in the dermis, it evokes pain, sometimes accompanied by itching. Stimulant actions on one or another type of nerve ending, including autonomic afferents and efferents, have been mentioned above as factors that contribute to the "flare" component of the triple response and to indirect effects of histamine on the bronchi and other organs. In the periphery, neuronal receptors for histamine are generally of the H_1 type (*see* Rocha e Silva, 1978; Ganellin and Parsons, 1982).

Mechanism of Action. The H_1 and H_2 receptors have been cloned and shown to belong to the superfamily of G protein–coupled receptors. H_1 receptors are coupled to phospholipase C, and their activation leads to formation of inositol-1,4,5-trisphosphate (IP_3) and diacylglycerols from phospholipids in the cell membrane; IP_3 causes a rapid release of Ca^{2+} from the endoplasmic reticulum. Diacylglycerols (and Ca^{2+}) activate protein kinase C, while Ca^{2+} activates Ca^{2+}/calmodulin-dependent protein kinases and phospholipase A_2 in the target cell to generate the characteristic response (*see* Chapter 2). H_2 receptors are linked to the stimulation of adenylyl cyclase and thus to the activation of cyclic AMP–dependent protein kinase in the target cell. In a species-dependent manner, adenosine receptors may interact with H_1 receptors. In the CNS of human beings, activation of adenosine A_1 receptors inhibits second messenger generation via H_1 receptors. A possible mechanism for this is interaction (termed *cross-talk*) between the G proteins to which the A_1 and H_1 receptors are coupled functionally (Dickenson and Hill, 1993).

In the smooth muscle of large blood vessels, bronchi, and intestine, the stimulation of H_1 receptors and the resultant IP_3-mediated release of intracellular Ca^{2+} leads to activation of the Ca^{2+}/calmodulin-dependent myosin light chain kinase. This enzyme phosphorylates the 20-kDa myosin light chain, with resultant enhancement of cross-bridge cycling and contraction (*see* Kamm and Stull, 1985; Somlyo *et al.*, 1988; Griendling and Alexander, 1990). The effects of histamine on sensory nerves also are mediated by H_1 receptors.

As mentioned above, the vasodilator effects of histamine are mediated by both H_1 and H_2 receptors that are located on different cell types in the vascular bed: H_1 receptors on the vascular endothelial cells and H_2 receptors on smooth muscle cells. Activation of H_1 receptors leads to increased intracellular Ca^{2+}, activation of phospholipase A_2, and the local production of endothelium-derived relaxing factor, which is nitric oxide (Palmer *et al.*, 1987). Nitric oxide diffuses to the smooth muscle cell, where it activates a soluble guanylyl cyclase and causes the accumulation of cyclic GMP. Stimulation of a cyclic GMP–dependent protein kinase and a decrease in intracellular Ca^{2+} are thought to be involved in the relaxation caused by this cyclic nucleotide. The activation of phospholipase A_2 in endothelial cells also leads to the formation of prostaglandins, predominantly prostacyclin (PGI_2); this vasodilator makes an important contribution to endothelium-mediated vasodilatation in some vascular beds.

The mechanism of cyclic AMP–mediated relaxation of smooth muscle is not entirely clear, but it is presumed to involve a decrease in intracellular Ca^{2+} (*see* Kamm and Stull, 1985; Taylor *et al.*, 1989). Cyclic AMP–mediated actions in the heart, mast cells, basophils, and other tissues also are understood incompletely, but the effects of histamine that are mediated by H_2 receptors obviously would be produced in the same fashion as those resulting from stimulation of beta-adrenergic receptors or other receptors that are linked to the activation of adenylyl cyclase.

Clinical Uses

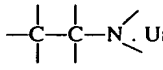
The practical applications of histamine are limited to uses as a diagnostic agent. Histamine *(histamine phosphate)* is used to assess nonspecific bronchial hyperreactivity in asthmatics and as a positive control injection during allergy skin testing.

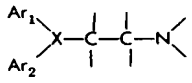
H_1-RECEPTOR ANTAGONISTS

Although antagonists that act selectively at the three types of histamine receptors have been developed, this discussion is confined to the properties and clinical uses of H_1 antagonists. Specific H_2 antagonists (*e.g.*, cimetidine, ranitidine) are used extensively in the treatment of peptic ulcers; these are discussed in Chapter 37. The properties of agonists and antagonists at H_3 receptors are discussed later in this chapter. Such agents are not yet available for clinical use.

History. Histamine-blocking activity was first detected in 1937 by Bovet and Staub in one of a series of amines with a phenolic ether function. The substance, 2-isopropyl-5-methylphenoxyethyldiethylamine, protected guinea pigs against several lethal doses of histamine, antagonized histamine-induced spasm of various smooth muscles, and lessened the symptoms of anaphylactic shock. This drug was too toxic for clinical use, but by 1944, Bovet and his colleagues had described pyrilamine maleate, which is still one of the most specific and effective histamine antagonists of this category. The discovery of the highly effective histamine antagonists diphenhydramine and tripelennamine soon followed (*see* Bovet, 1950; Ganellin, in Ganellin and Parsons, 1982). In the 1980s, nonsedating H_1-histamine-receptor antagonists were developed for treatment of allergic diseases.

By the early 1950s, many compounds with histamine-blocking activity were available to physicians, but they uniformly failed to inhibit certain responses to histamine, most conspicuously gastric acid secretion. The discovery by Black and colleagues of a new class of drugs that blocked histamine-induced gastric acid secretion provided new pharmacological tools with which to explore the functions of endogenous histamine. This discovery ushered in a major new class of therapeutic agents, the H_2 receptor antagonists, including cimetidine (TAGAMET), famotidine (PEPCID), nizatidine (AXID), and ranitidine (ZANTAC) (*see* Chapter 37).

Structure–Activity Relationship. All of the available H_1 receptor antagonists are reversible, competitive inhibitors of the interaction of histamine with H_1 receptors. Like histamine, many H_1 antagonists contain a substituted ethylamine moiety,  . Unlike histamine, which has a primary amino group and a single aromatic ring, most H_1 antagonists have a tertiary amino group linked by a two- or three-atom chain to two aromatic substituents and conform to the general formula:

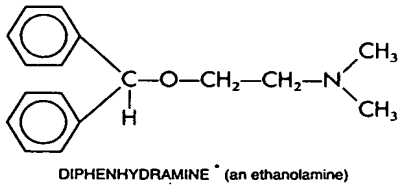


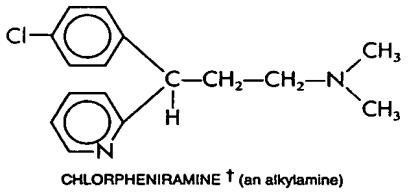
where Ar is aryl and X is a nitrogen or carbon atom or a —C—O— ether linkage to the beta-aminoethyl side chain. Sometimes the two aromatic rings are bridged, as in the tricyclic derivatives, or the ethylamine may be part of a ring structure. Other variations also are possible; for example, the piperidine H_1 antagonists *terfenadine* and *astemizole* have aromatic ring structures on either side of the carbon chain (Figure 25–2). (*See* Ganellin, in Ganellin and Parsons, 1982.)

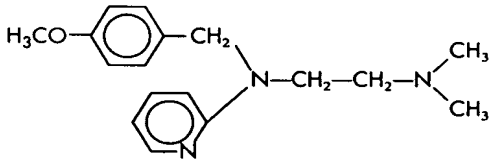
Pharmacological Properties

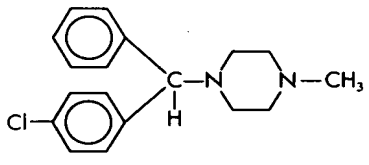
Most H_1 antagonists have similar pharmacological actions and therapeutic applications and can be discussed together conveniently. Their effects are largely predictable from knowledge of the responses to histamine that involve interaction with H_1 receptors.

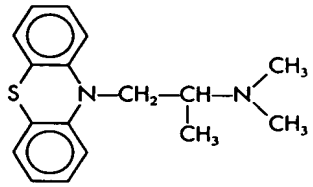
Smooth Muscle. H_1 antagonists inhibit most responses of smooth muscle to histamine. Antagonism of the constrictor action of histamine on respiratory smooth muscle is easily shown *in vivo* or *in vitro*. In guinea pigs, for example, death by asphyxia follows quite small doses of his-











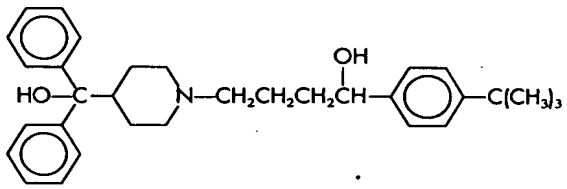


Figure 25–2. Representative H_1 antagonists.

*Dimenhydrinate is a combination of diphenhydramine and 8-chlorotheophylline in equal molecular proportions.
†Pheniramine is the same less Cl.
‡Tripelennamine is the same less H_3CO.
§Cyclizine is the same less Cl.

tamine, yet the animal may survive a hundred lethal doses of histamine if given an H_1 antagonist. In the same species, striking protection also is afforded against anaphylactic bronchospasm. This is not so in human beings, because allergic bronchoconstriction is caused primarily by mediators such as leukotrienes and platelet activating factor (*see* Chapter 26).

Within the vascular tree, the H_1 antagonists inhibit both the vasoconstrictor effects of histamine and, to a degree, the more rapid vasodilator effects that are mediated by H_1 receptors on endothelial cells. Residual vasodilation reflects the involvement of H_2 receptors on smooth muscle and can be suppressed only by the concurrent administration of an H_2 antagonist. Effects of the histamine antagonists on histamine-induced changes in systemic blood pressure parallel these vascular effects.

Capillary Permeability. H_1 antagonists strongly block the action of histamine that results in increased capillary permeability and formation of edema and wheal.

"Flare" and Itch. The "flare" component of the triple response and the itching caused by intradermal injection of histamine are two different manifestations of the action of histamine on nerve endings. H_1 antagonists suppress both.

Exocrine Glands. Gastric secretion is not inhibited at all by H_1 antagonists, and they suppress histamine-evoked salivary, lacrimal, and other exocrine secretions with variable responses. The atropine-like properties of many of these agents, however, may contribute to lessened secretion in cholinergically innervated glands and reduce ongoing secretion in, for example, the respiratory tree.

Immediate Hypersensitivity Reactions: Anaphylaxis and Allergy. During hypersensitivity reactions, histamine is one of many potent autacoids released (*see* above), and its relative contribution to the ensuing symptoms varies widely with species and tissue. The protection afforded by histamine antagonists obviously varies accordingly. In human beings, some phenomena, including edema formation and itch, are fairly well controlled; others, such as hypotension, are less so. Bronchoconstriction is reduced little, if at all (*see* Dahlén *et al.*, 1983).

Central Nervous System. The first-generation H_1 antagonists can both stimulate and depress the CNS. Stimulation occasionally is encountered in patients given conventional doses, who become restless, nervous, and unable to sleep. Central excitation also is a striking feature of poisoning, which not uncommonly results in convulsions, particularly in infants. Central depression, on the other hand, is the usual accompaniment of therapeutic doses of the older H_1 antagonists. Diminished alertness, slowed reaction times, and somnolence are common manifestations. Some of the H_1 antagonists are more likely to depress the CNS than others, and patients vary in their susceptibility and responses to individual drugs. The ethanolamines (*e.g.*, diphenhydramine; *see* Figure 25–2) are particularly prone to cause sedation.

The second-generation (nonsedating) H_1 antagonists (*e.g.*, terfenadine, astemizole, loratadine) are largely excluded from the brain when given in therapeutic doses, because they do not cross the blood–brain barrier appreciably (Sorkin and Heel, 1985; Krstenansky and Cluxton, 1987). Their effects on objective measures of sedation such as sleep latency, EEG, and standardized performance tests are similar to those of placebo (Simons and Simons, 1994). The lack of sedation is in contrast to the profound sedating side effects of first-generation antihistamines and may be of significant clinical benefit.

An interesting and useful property of certain H_1 antagonists is the capacity to counter motion sickness. This effect was first observed with *dimenhydrinate* and subsequently with *diphenhydramine* (the active moiety of dimenhydrinate), various piperazine derivatives, and *promethazine*. The latter drug has perhaps the strongest muscarinic blocking activity among these agents and is among the most effective of the H_1 antagonists in combating motion sickness (*see* below). Since scopolamine is the most potent drug for the prevention of motion sickness (*see* Chapter 7), it is possible that the anticholinergic properties of certain H_1 antagonists are largely responsible for this effect.

Anticholinergic Effects. Many of the first-generation H_1 antagonists tend to inhibit responses to acetylcholine that are mediated by muscarinic receptors. These atropine-like actions are sufficiently prominent in some of the drugs to be manifest during clinical usage (*see* below). The second-generation H_1 antagonists (*e.g.*, terfenadine, astemizole, loratadine) have no effect on muscarinic receptors (*see* Sorkin and Heel, 1985).

Local Anesthetic Effect. Some H_1 antagonists have local anesthetic activity, and a few are more potent than procaine. Promethazine (PHENERGAN) is especially active. However, the concentrations required for this effect are several orders higher than those that antagonize histamine.

Absorption, Fate, and Excretion. The H_1 antagonists are well absorbed from the gastrointestinal tract. Following oral administration, peak plasma concentrations are achieved in 2 to 3 hours and effects usually last 4 to 6 hours; however, some of the drugs are much longer acting (Table 25–1).

Table 25–1
Preparations and Dosage of Representative H_1-Receptor Antagonists*

CLASS AND NONPROPRIETARY NAME	TRADE NAME	DURATION OF ACTION, hours	PREPARATIONS†	SINGLE DOSE (ADULT)
First-Generation Agents				
Ethanolamines				
Carbinoxamine maleate	CARDEC;¶ others	3–6	L	4–8 mg
Clemastine fumarate	TAVIST, others	12–24	O, L	1.34–2.68 mg
Diphenhydramine hydrochloride	BENADRYL; others	4–6	O, L, I, T	25–50 mg
Dimenhydrinate	DRAMAMINE; others	4–6	O, L, I	50–100 mg
Ethylenediamines				
Pyrilamine maleate	NISAVAL	4–6	O	25–50 mg
Tripelennamine hydrochloride	PBZ	4–6	O	25–50 mg, 100 mg (sustained release)
Tripelennamine citrate	PBZ		L	37.5–75 mg
Alkylamines				
Chlorpheniramine maleate	CHLOR-TRIMETON; others	4–6	O, L, I	4 mg 8–12 mg (sustained release) 5–20 mg (injection)
Brompheniramine maleate	DIMETANE; others	4–6	O, L, I	4 mg 8–12 mg (sustained release) 5–20 (injection)
Piperazines				
Hydroxyzine hydrochloride	ATARAX; others	6–24	O, L, I	25–100 mg
Hydroxyzine pamoate	VISTARIL	6–24	O, L, I	25–100 mg
Cyclizine hydrochloride	MAREZINE	4–6	O, I	50 mg
Cyclizine lactate	MAREZINE	4–6	I	50 mg
Meclizine hydrochloride	ANTIVERT; others	12–24	O	12.5–50 mg
Phenothiazines				
Promethazine hydrochloride	PHENERGAN; others	4–6	O, L, I, S	25 mg
Second-Generation Agents				
Alkylamines				
Acrivastine	SEMPREX-D¶	6–8	O	8 mg
Piperazines				
Cetirizine hydrochloride‡		12–24	O	5–10 mg

Table 25–1 (continued)

CLASS AND NONPROPRIETARY NAME	TRADE NAME	DURATION OF ACTION, hours	PREPARATIONS†	SINGLE DOSE (ADULT)
Second-Generation Agents (cont.)				
Piperidines				
Astemizole	HISMANAL	>24	O	10 mg
Levocabastine hydrochloride	LIVOSTIN	16–24	T	One drop
Loratadine	CLARITIN	24	O	10 mg
Terfenadine	SELDANE	12–24	O	60 mg

*For a discussion of phenothiazines, *see* Chapter 18.
†Preparations are designated as follows: O, oral solids; L, oral liquids; I, injection; S, suppository; T, topical. Many H_1-receptor antagonists also are available in preparations that contain multiple drugs.
‡Cetirizine has mild sedating effects; it is not yet available in the United States.
¶Trade name drug also contains other medications.

Extensive studies of the metabolic fate of the older H_1 antagonists are limited. Diphenhydramine, given orally, reaches a maximal concentration in the blood in about 2 hours, remains at about this level for another 2 hours, and then falls exponentially with a plasma elimination half-time of about 4 hours. The drug is widely distributed throughout the body, including the CNS. Little, if any, is excreted unchanged in the urine; most appears there as metabolites. Other first-generation H_1 antagonists appear to be eliminated in much the same way (*see* reviews by Witiak and Lewis, 1978; Paton and Webster, 1985).

Information on the concentrations of these drugs achieved in the skin and mucous membranes is lacking. However, significant inhibition of "wheal-and-flare" responses to the intradermal injection of histamine or allergen may persist for 36 hours or more after treatment with some longer-acting H_1 antagonists, even when concentrations of the drugs in plasma are very low. Such results emphasize the need for flexibility in the interpretation of the recommended dosage schedules (*see* Table 25–1); less frequent dosage may suffice. Like many other drugs that are metabolized extensively, H_1 antagonists are eliminated more rapidly by children than by adults and more slowly in those with severe liver disease. H_1-receptor antagonists are among the many drugs that induce hepatic microsomal enzymes, and they may facilitate their own metabolism (*see* Paton and Webster, 1985; Simons and Simons, 1988).

The second-generation H_1 antagonists astemizole, loratadine, and terfenadine are rapidly absorbed from the gastrointestinal tract and metabolized in the liver to active metabolites by the hepatic microsomal P450 system (Simons and Simons, 1994). Consequently, metabolism of these drugs can be affected by competition for the P450 enzymes by other drugs. This alteration of metabolism can be clinically significant (*see* "Polymorphic Ventricular Tachycardia," below). Cetirizine, an active metabolite of hydroxyzine, and acrivastine also are well absorbed but primarily are excreted renally in the unmetabolized form (Brogden and McTavish, 1991; Spencer *et al.*, 1993; Barnes *et al.*, 1993).

Side Effects. ***Sedation and Other Common Adverse Effects.*** The side effect with the highest incidence in the first-generation H_1 antagonists, which is not a feature of the second-generation agents, is sedation (Carruthers *et al.*, 1978). Although sedation may be a desirable adjunct in the treatment of some patients, it may interfere with the patient's daytime activities. Concurrent ingestion of alcohol or other CNS depressants produces an additive effect that impairs motor skills (Roehrs *et al.*, 1993). Other untoward reactions referable to central actions include dizziness, tinnitus, lassitude, incoordination, fatigue, blurred vision, diplopia, euphoria, nervousness, insomnia, and tremors.

The next most frequent side effects involve the digestive tract and include loss of appetite, nausea, vomiting, epigastric distress, and constipation or diarrhea. Their incidence may be reduced by giving the drug with meals. H_1 antagonists appear to increase appetite and cause weight gain in rare patients. Other side effects that apparently are caused by the antimuscarinic actions of some of the first-generation H_1-receptor antagonists include dryness of the mouth and respiratory passages, sometimes inducing cough, urinary retention or frequency, and dysuria. These effects are not observed with second-generation H_1 antagonists, terfenadine, astemizole, and loratadine.

Polymorphic Ventricular Tachycardia. Rarely, terfenadine and astemizole cause prolongation of the QTc interval with resultant polymorphic ventricular tachycardia (*torsades de pointes*; *see* Chapter 35). The mechanism underlying terfenadine-related cases is understood and seems similar for astemizole. *Torsades de pointes* can occur when terfenadine is taken in higher-than-recommended dosages or in situations in which hepatic metabolism is impaired either by disease or by coadministration of drugs that inhibit CYP3A4, the specific cytochrome P450 thought to be responsible for terfenadine metabolism (Woosley *et al.*, 1993; Honig *et al.*, 1993). The result of overdosage or impaired metabolism is incomplete first-pass hepatic conversion of the parent drug to the carboxy metabolite. The carboxy metabolite is responsible for the clinical antihistamine actions. The parent drug, but not the metabolite, blocks delayed rectifier potassium channels, as do sotalol and quindine (*see* Chapter 35). Preexistent prolonged QTc intervals or significant hepatic dysfunction are risk factors. The drugs that most commonly inhibit CYP3A4-mediated terfenadine metabolism are the macrolide antibiotics [most notably erythromycin ethylsuccinate (E.E.S., others) and clarithromycin (BIAXIN)] and antifungal agents [most notably ketoconazole (NIZORAL) and itraconazole (SPORANOX)]. Azithromycin (ZITHROMAX) and fluconazole (DIFLUCAN), which are predominantly excreted unmetabolized in the urine, have not been associated with impaired metabolism of terfenadine. The study of drug interactions involving second-generation H_1 antagonists is evolving rapidly, and it seems certain that the list of contraindicated drugs for coadministration will increase.

Although also metabolized by CYP3A4, the second-generation H_1 antagonist loratadine does not appear to be associated with this toxicity, even with co-administration of inhibitors (Woosley and Darrow, 1994). Cetirizine and acrivistine are primarily excreted unmetabolized by the kidney and have been shown to not increase the QTc interval in normal human subjects (Sanders *et al.*, 1992; Sale *et al.*, 1994).

Mutagenicity. Results of one short-term study (Brandes *et al.*, 1994) with an unconventional mouse model indicated that melanoma and fibrosarcoma tumor lines had an increased rate of growth when injected into mice receiving certain H_1 antagonists. However, conventional studies with animals and clinical experience do not suggest carcinogenicity for H_1 receptor antagonists (Food and Drug Administration, 1994).

Other Adverse Effects. Drug allergy may develop when H_1 antagonists are given orally, but more commonly it results from topical application. Allergic dermatitis is not uncommon; other hypersensitivity reactions include drug fever and photosensitization. Hematological complications such as leukopenia, agranulocytosis, and hemolytic anemia are very rare. Teratogenic effects have been noted in response to piperazine compounds, but extensive clinical studies have not demonstrated any association between the use of such H_1 antagonists and fetal anomalies in human beings. Since H_1 antagonists interfere with skin tests for allergy, they must be withdrawn well before such tests are performed.

In acute poisoning with H_1 antagonists, their central excitatory effects constitute the greatest danger. The syndrome includes hallucinations, excitement, ataxia, incoordination, athetosis, and convulsions. Fixed, dilated pupils with a flushed face, together with sinus tachycardia, urinary retention, dry mouth, and fever, lend the syndrome a remarkable similarity to that of atropine poisoning. Terminally, there is deepening coma with cardiorespiratory collapse and death, usually within 2 to 18 hours. Treatment is along general symptomatic and supportive lines.

Available H_1 Antagonist Agents. Below are summarized the therapeutic and side effects of a number of H_1 antagonists, based on their chemical structure. Representative preparations are listed in Table 25–1.

Ethanolamines (Prototype: Diphenhydramine). The drugs in this group possess significant antimuscarinic activity and have a pronounced tendency to induce sedation. About half of those who are treated with conventional doses of these drugs experience somnolence. The incidence of gastrointestinal side effects, however, is low with this group.

Ethylenediamines (Prototype: Pyrilamine). These include some of the most specific H_1 antagonists. Although their central effects are relatively feeble, somnolence occurs in a fair proportion of patients. Gastrointestinal side effects are quite common.

Alkylamines (Prototype: Chlorpheniramine). These are among the most potent H_1 antagonists. The drugs are not so prone as some H_1 antagonists to produce drowsiness and are among the more suitable agents for daytime use; but again, a significant proportion of patients do experience sedation. Side effects involving CNS stimulation are more common in this than in other groups.

Piperazines. The oldest member of this group, *chlorcyclizine,* has a more prolonged action and produces a comparatively low incidence of drowsiness. *Hydroxyzine* is a long-acting compound that is widely used for skin allergies; its considerable central-depressant activity may contribute to its prominent antipruritic action. *Cetirizine* is an active metabolite of hydroxyzine that does not significantly penetrate the central nervous system and has less propensity to sedation. There are plans for its release in the United States in the near future. Cyclizine and meclizine have been used primarily to counter motion sickness, although promethazine and diphenhydramine (dimenhydrinate) are more effective (as is scopolamine; *see* below).

Phenothiazines (Prototype: Promethazine). Most drugs of this class are H_1 antagonists and also possess considerable anticholinergic activity. Promethazine, which has prominent sedative effects, and its many congeners are now used primarily for their antiemetic effects (*see* Chapter 38).

DRUG INFORMATION NOTES

Ex E1

Astemizole and Terfenadine-Induced Cardiovascular Effects

Compared to traditional antihistamines such as diphenhydramine and chlorpheniramine, astemizole and terfenadine, two new histamine$_1$-receptor antagonists, have not been associated with many adverse effects. Sedation and anticholinergic effects do not appear to be a problem with these newer antihistamines since they are not very lipid soluble and do not cross the blood-brain-barrier. In overdose, the traditional antihistamines cause central anticholinergic effects such as seizures, muscle tremors, respiratory arrest, multifocal premature ventricular contractions, left-bundle branch block, metabolic acidosis and hypotension.[1] Overdoses with astemizole and terfenadine appear to be complicated by torsade de pointes as reported in several recent cases.

Torsade de pointes is a form of ventricular tachycardia characterized by gradual oscillation around the baseline of the peaks of successive QRS complexes and prolongation of the QT interval leading afflicted patients to present with recurrent dizziness and syncope. Drug-induced torsade de pointes has been attributed to more than 20 agents including amiodarone, disopyramide, propranolol, quinidine, amitriptyline, thioridazine and more recently, astemizole and terfenadine.[2,3]

In one case,[4] a 16-year old presented to the emergency department after swallowing 20 tablets of astemizole (total dose 200 mg). Eight hours after the overdose she developed spontaneous ventricular tachycardia which was unsuccessfully treated with lidocaine and amiodarone. A prolonged QT interval was noted and successful treatment with isoproterenol was begun. Upon discharge, she was well with a normal QT interval.

In another case,[5] a total dose of 250 mg of astemizole was ingested by a 16-year old. Upon presentation to the emergency department, an electrocardiogram (ECG) showed sinus tachycardia with a prolonged QT interval. During the next 48 hours the QT interval returned to normal without treatment. Three other cases[6,7,8] of astemizole-induced torsade de pointes in adults have been published; in two cases, recovery was complete after the drug was stopped and in the other case the premature ventricular contractions and ventricular tachycardia rapidly resolved following administration of magnesium sulfate.

A recent report[9] documented six cases of accidental astemizole poisoning in children aged one to three years. The amount ingested varied from 30 mg to 200 mg. A prolonged QT interval was found in five children. As well, one patient developed severe ventricular arrhythmias.

Terfenadine has also been associated with torsade de pointes. In one case,[10] a 21-year old developed generalized convulsions as well as prolonged QT intervals. Another patient ingested both astemizole (700 mg) and terfenadine (1200 mg).[11] The main sign of intoxication was torsade de pointes. The patient was discharged without any permanent sequelae.

Torsade de pointes has also been documented[12] in a 39-year old woman who ingested a therapeutic dose of terfenadine 60 mg twice daily in conjunction with ketoconazole 200 mg twice daily. She developed episodes of syncope and lightheadedness; an ECG showed a prolonged QT interval. As well, terfenadine and metabolite concentrations were remarkably elevated. It was suggested that ketoconazole may have elevated terfenadine plasma levels via inhibition of the P-450 metabolic pathway. Terfenadine may also interact with other drugs that inhibit P-450 metabolism, for example, cimetidine or erythromycin.

In summary, astemizole and terfenadine have caused torsade de pointes in susceptible patients. The limited amount of published information does not permit the development of guidelines regarding management or how long to monitor these patients. Isoproterenol is the drug most commonly used to treat torsade de pointes, although overdrive pacing remains the treatment of choice. As well, pharmacists and physicians should be aware that drugs which inhibit the cytochrome P-450 pathway (eg. ketoconazole, cimetidine, erythromycin) may inhibit terfenadine clearance and lead to toxicity. EX

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que possible. La CPP attirerait-elle autant de participants si elle se tenait dans une plus petite ville que Toronto? Est-il possible de réduire le coût en choisissant un autre hôtel? Les participants seraient-ils prêts à accepter un compromis quant aux installations afin de réduire le coût? Les participants éventuels s'inscriraient-ils à la conférence si celle-ci se tenait dans un hôtel situé en dehors du centre d'une ville? Les programmes éducatifs des sections souffriraient-ils si la CPP se déplaçait dans leur ville?

Voilà quelques-unes des questions qui seront abordées par le groupe de travail présidé par M. Larry Legare. Si vous désirez donner votre avis concernant le lieu de la CPP dans l'avenir, veuillez communiquer avec lui à l'adresse suivante :

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Les conférences offrent bien des avantages, mais pour en profiter, il faut participer. Il est parfois utile d'écouter les autres parler de leurs difficultés pour mettre en contexte ses propres dilemmes professionnels. En plus de glaner de nouvelles idées et de nouvelles approches, vous serez porté par un sentiment de camaraderie et d'enrichissement professionnel dont la valeur ne peut se mesurer en monnaie sonnante!

Au plaisir de vous rencontrer à la prochaine conférence!

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These results, together with those of Lloyd and colleagues,[4] indicate that the IFN-γ system in peripheral cells of the immune system is not activated in CFS. However, they do not exclude the possibility of locally increased production of this lymphokine in the central nervous system.

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ASTEMIZOLE-INDUCED TORSADE DE POINTES

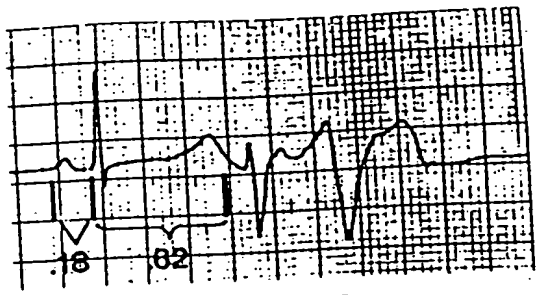
SIR,—We report a 15-year-old girl who collapsed outdoors, recovering within 5 min. No seizure activity was noted. Soon after emergency admission, she collapsed again. She had extreme pallor, an irregular heart-rate of 44/min, and oedema and crusting of the nasal mucosa. An electrocardiogram (ECG) showed multiform premature ventricular contractions and prolonged QT interval, with first-degree atrioventricular block (figure). The patient was admitted to intensive care for monitoring. 5 h later, she had two episodes of torsade de pointes associated with loss of consciousness. She was treated with chest compression, oxygen, lignocaine, and propranolol. No further arryhthmias occurred and the QT interval returned to normal over the next 6 days, at which time the patient was discharged.

The patient had a history of allergic rhinitis, treated with astemizole 10 mg daily for 10 weeks. Her last dose of astemizole had been taken 28 h before admission. She gave a history of recurrent syncope for 3 days preceding admission. She denied astemizole overdose, did not use any other medication, and had no history of smoking, drinking, or substance abuse. She and her immediate family had no history of cardiac problems, deafness, seizures, or sudden death.

The patient's serum electrolytes and hepatic function were normal. Toxic drug screens were negative. The serum concentration of astemizole plus hydroxylated astemizole metabolites 38 h after the ingestion of the last astemizole dose was 44·6 ng/ml, decreasing to 1·8 ng/ml 6 weeks later. The serum elimination half-life was 13·5 days. The epicutaneous wheal response to histamine, monitored daily for 7 days then weekly, remained suppressed until 7 weeks after the last dose of astemizole.

The patient received propranolol at home for 7 weeks and remained symptom-free. Weekly ECGs demonstrated normal sinus rhythm. 7 weeks after the episodes of ventricular tachycardia, when the wheal response to histamine had returned, she was readmitted and propranolol was withdrawn uneventfully during cardiac monitoring. The corrected QT interval 48 h after cessation of propranolol was 0·44. She has remained well and takes no medication except for intranasal beclomethasone dipropionate.

The mean serum elimination half-life of astemizole in adolescent patients taking 10 mg per day for 12 weeks is 11·8 days, and the mean pre-dose steady-state serum concentration of astemizole plus hydroxylated metabolites is 3·8 (SD 2·3) ng/ml (J. Heykants, Janssen). In adults, after a two-week course of astemizole (30 mg daily for 3 days then 10 mg daily for 12 days), the wheal response to histamine remains significantly suppressed for 6 weeks, and the flare response remains significantly suppressed for 7 or more weeks.[1] This same regimen results in pre-dose serum concentrations of astemizole plus hydroxylated metabolites of 2·72–3·63 ng/ml at the end of the second week of treatment, and does not produce changes in heart rate, blood pressure, ECG, or systolic intervals in normal adult volunteers.[2]



Admission ECG.

Long PR interval (0·18 s) and prolonged QT interval (0·62 s), followed by premature ventricular couplet. Corrected QT interval was 0·62 as sinus rate was 60/min. Critically timed premature ventricular contractions often initiate torsade de pointes in patients with prolonged QT interval.

QT interval prolongation and torsade de pointes may have a familial, metabolic, neurological, or medication-induced aetiology. H_1-receptor antagonists such as astemizole are structurally related to tricyclic antidepressants, which are known provokers of torsade de pointes. Stimulation of cardiac histamine receptors (H_1 and H_2) increases cyclic AMP via activation of adenylate cyclase and phosphorylase, producing both increased inotropic and chronotropic effects. The mechanisms of the repolarisation changes leading to QT prolongation are not fully understood. Astemizole provoked this complication in an adolescent who had overdosed with 200 mg (serum astemizole plus hydroxylated metabolite concentrations of 79·9 ng/ml, 10 h later).[3] Another adolescent who overdosed with 200 mg astemizole had no cardiac problems and was symptom-free except for slight sedation.[4]

In our patient, the distribution phase half-life of 13·4 h and the elimination phase half-life of 13·5 days for astemizole plus hydroxylated metabolites are similar to values in the adolescent who had cardiac problems after overdose.[3] Although our patient denied overdose and furthermore had fainted in the 3 days before cardiac arrest, the data are more consistent with ingestion of a 200–300 mg single dose than with chronic ingestion of 10 mg daily for 10 weeks in a patient with normal hepatic function and no predisposition to drug accumulation.

Treatment with astemizole, a very long-acting H_1-receptor antagonist, should be considered in the differential diagnosis of prolonged QT interval and ventricular tachyarrhythmias. Physicians should be aware that astemizole can cause torsade de pointes in rare cases. The non-prescription status of astemizole in some countries requires review.

We thank Dr A. Raoult, Janssen Pharmaceutica, Mississauga, Ontario for cooperation; and Dr J. Heykants, Janssen Pharmaceutica, Beerse, Belgium, for assay of serum astemizole plus hydroxylated metabolites.

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tant (rē-ak'tant). A substance taking part in a chemical tion.

te phase r.'s, a group of proteins that are produced and/or ased in increased concentrations during the acute phase reac- including fibrinogen; C-reactive protein; complement pro- s B, C3, C4; α_2-acid glycoprotein, serum amyloid A, protein- inhibitors, etc.

REACTION

c·tion (rē-ak'shŭn). **1.** The response of a muscle or other ing tissue or organism to a stimulus. **2.** The color change ected in litmus and certain other organic pigments by contact h substances such as acids or alkalies; also the property that h substances possess of producing this change. **3.** In chemistry, intermolecular action of two or more substances upon each er, whereby these substances are caused to disappear, new es being formed in their place (chemical r.). **4.** In immunology, vivo or in vitro action of an antibody on a specific antigen, with without the involvement of a complement or other components the immunologic system. [L. *re-*, again, backward, + *actio*, tion]

celerated r., a response occurring in a shorter time than expect- the cutaneous manifestations occurring during the period be- een the second and tenth day following smallpox vaccination; cause it is intermediate between a primary r. and an immediate it is regarded as evidence of some degree of resistance. SYN accinoid r.

id r., (1) any test by which an acid r. is recognized, such as the hange of blue litmus paper to red; (2) an excess of hydrogen ions ver hydroxide ions in aqueous solution indicated by a pH value ss than 7 (at 22°C). Cf. dissociation *constant* of water.

cute phase r., refers to the changes in synthesis of certain roteins within the serum during an inflammatory response; this esponse provides rapid protection for the host against microor- anisms via nonspecific defense mechanisms. SYN acute phase esponse.

cute situational r., SYN stress r.

cute stress r., SYN anxiety r.

dverse r., any undesirable or unwanted consequence of a pre- entive, diagnostic, or therapeutic procedure or regimen.

larm r., the various phenomena, e.g., stimulated endocrine ac- ivity, which the body exhibits as an adaptive response to injury r stress; first phase of the general adaptation syndrome.

ldehyde r., the r. of the indole derivatives with aromatic alde- ydes; e.g., tryptophan and *p*-dimethylaminobenzaldehyde in H_2SO_4 give a red-violet color useful in assaying proteins for tryptophan content. SYN Ehrlich r.

lkaline r., (1) any test by which an alkaline r. is recognized, uch as the change of red litmus paper to blue; (2) an excess of ydroxide ions over hydrogen ions in aqueous solution as indi- ated by a pH value >7 (at 22°C). Cf. dissociation *constant* of water. SYN basic r.

llergic r., a local or general r. of an organism following contact with a specific allergen to which it has been previously exposed nd sensitized; immunologic interaction of endogenous or exoge- ous antigen with antibody or sensitized lymphocytes gives rise to nflammation or tissue damage. Allergic r.'s are classified into our major types: type I, anaphylactic and IgE dependent; type II, ytotoxic; type III, immune-complex mediated; type IV, cell me- iated (delayed). SYN hypersensitivity r.

mphoteric r., a double r. possessed by certain fluids that have a ombination of acid and alkaline properties.

namnestic r., augmented production of an antibody due to pre- ious exposure of the subject to the same antigen.

naphylactic r. (an'a-fĭ-lak'tik), SYN anaphylaxis.

naplerotic r., SEE anaplerotic.

ntigen-antibody r. (AAR), the reversible phenomenon, occurring in vitro or in vivo, of an antibody combining with an antigen of the type that stimulated the formation of the antibody, thereby resulting in agglutination, precipitation, complement fixation, greater susceptibility to ingestion and destruction by phagocytes, or neutralization of exotoxin. SEE ALSO skin *test*.

anxiety r., a psychologic r. or experience involving the apprehension of danger accompanied by a feeling of dread and such physical symptoms as an increase in the rate of breathing, sweating, and tachycardia, in the absence of a clearly identifiable fear stimulus; when chronic, it is called generalized anxiety *disorder*. SEE ALSO panic *attack*. SYN acute stress r.

Arias-Stella r., SYN Arias-Stella *phenomenon*.

arousal r., change in pattern of the brain waves when the subject is suddenly awakened and becomes alert.

Arthus r., (1) SYN Arthus *phenomenon*; (2) Arthus-type r.; r. in humans and other species that results from the same basic immunologic (allergic) mechanism that evokes, in the rabbit, the typical Arthus phenomenon. SEE ALSO immune complex *disease*.

Ascoli r., a method for confirming the diagnosis of anthrax by means of a precipitin r., which indicates the presence of heat-stable *Bacillus anthracis* antigen in the extracted tissue.

associative r., a secondary or side r.

basic r., SYN alkaline r.

Bence Jones r., the classic means of identifying Bence Jones protein, which precipitates when urine (from patients with this type of proteinuria) is gradually warmed to 45–70°C and redissolves as the urine is heated to near boiling; as the specimen cools, the Bence Jones protein precipitates in the indicated range of temperature and redissolves as the temperature of the specimen becomes less than 30–35°C.

Berthelot r., the r. of ammonia with phenol-hypochlorite to give indophenol; the principle is used to analyze ammonia concentration in body fluids.

bi bi r., a r. catalyzed by a single enzyme in which two substrates and two products are involved; the ping-pong mechanism may be involved in such a r. Cf. mechanism.

Bittorf r., in cases of renal colic, pain radiating to the kidney upon squeezing the testicle or pressing the ovary.

biuret r., the formation of biuret that gives a violet color as a result of the r. of a polypeptide of more than three aminoacyl residues with $CuSO_4$ in strongly alkaline solution; dipeptides and amino acids (except histidine, serine, and threonine) do not so react; used for the detection and quantification of polypeptides, or proteins, in biologic fluids.

Bloch r., SYN dopa r.

Bordet and Gengou r., SEE complement *fixation*.

Brunn r., the increased absorption of water through the skin of the frog when the animal is injected with pituitrin and immersed in water; one of the physiologic reactions used to study and classify posterior pituitary polypeptides and their analogues.

Burchard-Liebermann r., a blue-green color produced by acetic anhydride with cholesterol (and other sterols) dissolved in chloroform, when a few drops of concentrated sulfuric acid are added. SEE Liebermann-Burchard *test*.

Cannizzaro r., formation of an acid and an alcohol by the simultaneous oxidation of one aldehyde molecule and reduction of another; a dismutation: $2RCHO \rightarrow RCOOH + RCH_2OH$; when the aldehydes are not identical, this is referred to as a crossed Cannizzaro reaction.

capsular precipitation r., SYN quellung r. (2).

Carr-Price r., the r. of antimony trichloride with vitamin A to yield a brilliant blue color; this r. forms the basis of several quantitative techniques for the determination of vitamin A.

catalatic r., decomposition of H_2O_2 to O_2 and H_2O, as in the action of catalase; analogous to peroxidase r.

catastrophic r., the disorganized behavior that is the response to a severe shock or threatening situation with which the person cannot cope.

cell-mediated r., immunologic r. of the delayed type, involving chiefly T lymphocytes, important in host defense against infection, in autoimmune diseases, and in transplant rejection. SEE ALSO skin *test*.

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Skin reactions to hydroxyzine

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Sensitivity to histamine H1-antagonists has mainly been observed with phenothiazine and ethylenediamine, and is very rare with hydroxyzine. We report 3 cases of sensitization to hydroxyzine, which was prescribed to treat urticaria and atopic dermatitis. A generalized maculopapular eruption appeared shortly after taking the drug. Patch tests with Atarax® tablet were positive +++, and ++ or +++ with different dilutions of hydroxyzine. Patch tests with ethylenediamine, piperazine and other antihistamines were negative; therefore, there is no cross-allergy. We believe these rapid systemic reactions to hydroxyzine after the initial dose may have been due to prior systemic sensitivity to this drug, which cannot be used topically. Allergy to antihistamines must be considered when cutaneous lesions worsen on such therapy.

Key words: hydroxyzine; histamine H1-antagonists; antihistamine drug eruption; adverse drug reaction; lack of cross-sensitivity.

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Adverse drug reactions to histamine H1–antagonists are rare. This chemical family is divided into several groups ; phenothiazine and ethylenediamine subgroups are the main potential allergens (1). Allergy to hydroxyzine, which is close in structure to piperazine, has rarely been reported (2). We report 3 cases.

Patients and Methods

Patient no. 1

In December 1992, a 65–year-old woman was referred to our department with an adverse cutaneous drug reaction to Lariam® (mefloquine: Roche, Neuilly-Sur-Seine, France). To calm the pruritus, treatment with Atarax® tablets 100 mg/day (hydroxyzine: UCB Pharma, Nanterre, France) was introduced. At that time, we were surprised that, although Lariam® had been stopped the eruption healed so slowly. In January 1993, Atarax® was withdrawn. In April 1993, the patient developed urticaria which was treated with Atarax® 25 mg/day and Clarityne® tablets 10 mg/day. 12 h later, a generalised maculopapular eruption appeared. The eruption healed after discontinuance of Atarax® and Clarityne®. Urticaria was also cured. Patch testing was performed in January 1994 and June 1994.

Patient no. 2

For 20 years, a 36–year-old woman had eczema of the face and hands. She was atopic but she also had contact dermatitis from colophony, balsam of Peru, fragrance and oakmoss. Recurrences of eczema were treated with topical corticosteroids and several antihistamines, including Atarax®. In July 1995, she presented with an acute eczema of the face treated with Atarax® 25 mg/day and Noctran® (clorazepate dipotassique, acepromazine, aceprometazine: Menarini, Rungis, France). 3 days later, a generalized maculopapular eruption appeared. This eruption healed after discontinuation of Atarax® and Noctran®. Patch testing was performed in September 1995 and April 1996.

Patient no. 3

In December 1995, a 35–year-old woman was admitted at risk of premature labor. She was treated with Natisédine® (phenobarbital, passiflore: Procter & Gamble pharmaceuticals, Neuilly-sur-Seine, France), Pré-Par® (ritodrine: Solvay Pharma, Suresnes, France) and Salbumol® (salbutamol: Glaxo Wellcome, Paris, France) before delivery. She also took Maxilase-Bacitracine® tablets (alpha-amylase, bacitracin: Sanofi Winthrop, Gentilly, France) for a sore throat. 3 days later she presented with urticaria which was treated with Atarax® 25 mg/day and Polaramine® 2 mg/day (dexchlorpheniramine: Schering-Plough, Levallois-Perret, France). As soon as she started antihistamines, her urticaria worsened and became more pruriginous. 2 days later, she underwent a caesarian operation and other drugs were prescribed:

Syntocinon® (oxytocin: Sandoz, Rueil-Malmaison, France), Pro-Dafalgan® (propacetamol: UPSA, Rueil-Malmaison, France), Zinnat® (cefuroxime: Glaxo Wellcome, Paris, France), Profénid® (ketoprofen: Specia, Paris, France), Fragmine® (dalteparin sodium: Pharmacia, Saint-Quentin-Yvelines, France) and Parlodel® (bromocriptine: Sandoz, Rueil-Malmaison, France). After the delivery, a morbilliform eruption appeared. 7 days later, the patient presented with a fever of 40°C, adenopathy and erythroderma. Multiple microbiologic cultures and viral serologies eliminated infectious disease. 5 days after the discontinuance of all drugs except Parlodel®, the cutaneous lesions cleared.

Skin testing

Using Finn Chambers (Epitest, Tuusula, Finland), the 3 patients were tested with the European standard series, their topical medicaments and systemic drugs. All drugs, including Atarax®, were tested with a crushed tablet diluted in water. Prick tests were also performed with Atarax® tablets. A few months later, other patch tests were performed with different dilutions (2%, 5%, 10% aq.) of hydroxyzine hydrochloride and all the other components of Atarax® tablets: macrogol 6000 (5% aq.), colloidal silica (5% aq.), povidone K30 (5% aq.), microcrystalline cellulose (5% aq.), magnesium stearate (5% aq.), eudragit E (20% pet.), lactose (20% aq.), talc (as is) and titanium dioxide (5% aq.). They were also patch tested with piperazine (1% pet.), ethylenediamine (1% pet.), and triethanolamine (2.5% pet.) marketed by Isotec (Saint Quentin, France) and 6 other histamine H1-antagonists: dexchlorpheniramine (Polaramine®), loratadine (Clarityne®), chlorpromazine (Phénergan®), mequitazine (Primalan®), terfenadine (Teldane®) and cetirizine (Zyrtec®). Reading was performed 3 days later according to international convention. 190 control subjects were tested with Atarax® tablets.

Results

All 3 patients gave positive patch tests (+++) with Atarax® tablet and with the different dilutions of hydroxyzine (+++ or ++) (Fig. 1). All the other components of Atarax® tablet, and also the prick tests with Atarax®, were negative. Piperazine, ethylenediamine, triethanolamine and the 6 other antihistamines were negative. Patient no. 2 had a positive patch test (+) to tomato. Patient no. 3 had doubtful reactions to Natisédine® and Zinnat®. The 190 control subjects had negative patch tests with Atarax® tablet.

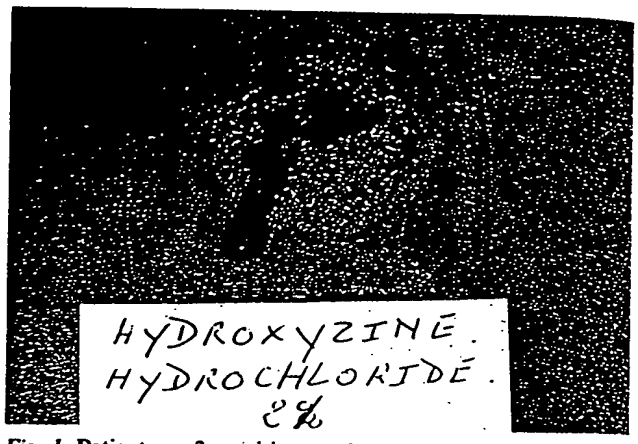

Fig. 1. Patient no. 3: positive patch test to hydroxyzine hydrochloride (2% aq.)

Discussion

Hydroxyzine is a 1st generation histamine H1–antagonist that is derived from piperazine. This drug also blocks muscarinic-cholinergic, α-adrenergic and 5-hydroxytryptaminergic receptors. It is an antiallergic drug but also a tranquillizer, a hypnotic and used as preoperative medication.

The 1st generation of histamine H1-antagonists is divided into 6 subgroups: alkylamine, ethanolamine, ethylenediamine, piperazine, piperadine and phenothiazine. They all have the basic structure of histamine modified by substitution on the imidazole ring. They have effects especially on H1-mediated reactions (3). Their side-effects are sedation, daytime drowsiness and neuroleptic effects. They also block other receptors : urinary retention, nasal stuffiness and blurring of vision are related to their anticholinergic properties (4). These adverse reactions have limited the use of the classical antihistamines. There are new 2nd generation H1-receptor antagonists that are more selective and less sedative. However, hydroxyzine is still widely used because of its availability in formulation for parenteral use, relatively high benefit-risk ratio and suitability for 1× daily administration.

Skin sensitization occurs with the use of ethylenediamine and phenothiazines (5–7), the latter also producing photosensitivity (8–10). Recently, skin reaction to terfenadine has been reported (11). Like all antihistamines, hydroxyzine can induce cutaneous sensitization, though very few cases have been reported (2, 4). The generalized polymorphous rash that our patients had after taking hydroxyzine was very difficult to differentiate from the initial one. All 3 patients initially presented with urticaria (nos. 1, 3) or eczema (no. 2), which necessitated the prescription of drugs including

Atarax®. Secondarily, another iatrogenic cutaneous eruption appeared; Atarax®, but also other drugs, could have been involved in the genesis of this 2nd eruption. Allergy to hydroxyzine was demonstrated by the positivity of patch tests (12). These tests seem reliable because there was no false positive reaction in 190 control subjects.

Topical and systemic use of antihistamines can both induce skin sensitization. In our patients it was probably systemic sensitization because topical hydroxyzine does not exist. Besides, 2 of them had taken Atarax® a few months before. Topical use of H1-antagonists often produces local sensitization. Cross-reactions between ethylenediamine, present in some creams, and the ethylenediamine H1-antagonists aminophylline and piperazine have been reported (13, 14). Fisher (1) has shown that there is cross-allergy between different groups of antihistamines because of their structural similarities. Therefore, patients sensitized to hydroxyzine, which is a piperazine antihistamine, are also sensitized to ethylenediamine. In contrast to other published cases, our patients had positive patch tests to hydroxyzine but negative tests with piperazine, ethanolamine and ethylenediamine. Many 1st and 2nd generation antihistamines' tests are negative, including cetirizine, which differs from hydroxyzine by an acid function. Allergy to antihistamines must be considered when cutaneous lesions worsen on antihistamine therapy.

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Warfarin treatment of chronic idiopathic urticaria and angio-oedema

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Summary

Background Chronic idiopathic urticaria is a disabling condition that does not always respond to antihistamine drugs and other agents are sometimes needed to control disease activity. Warfarin has demonstrated efficacy in single unblinded case studies [1] but has been dismissed by others [2].

Objective We investigated the effect of warfarin treatment in eight patients with chronic idiopathic urticaria unresponsive to antihistamines in an open study. Six of the eight patients responded to treatment and three had a dramatic response. These three were included in a double-blind placebo-controlled trial of warfarin therapy to confirm significant benefit from treatment.

Methods The three warfarin responders had their stable warfarin dose encapsulated and placebo capsules were provided. A double-blind placebo-controlled crossover trial was performed on each patient. Visual analogue scores recorded disease activity.

Results Comparison of visual analogue scores showed a significant benefit while on warfarin with a reduction in pruritus and angio-oedema.

Conclusion This is the first double-blind placebo-controlled study to show a response of chronic idiopathic urticaria to warfarin. The mechanisms of action are unclear and require further study.

Keywords: treatment, urticaria, warfarin

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Introduction

Chronic idiopathic urticaria is a common disorder characterized by recurrent urticarial weals of unknown origin for 3 or more month's duration. Typically there is a variable response to antihistamines and a tendency to spontaneous resolution; many patients are adequately treated by general practitioners. However there is a subgroup of patients in whom there is no tendency to improvement with time and who suffers severe urticaria often accompanied by angio-oedema, which is unresponsive to antihistamines. Some of these patients have an associated underlying disorder but most have no detectable abnormality. Severe urticaria is a debilitating condition and nonantihistamine treatments are limited by their lack of efficacy and/or risk of side effects. It has been suggested that some patients may respond to warfarin therapy [1] but this was questioned in a further study which showed no improvement [2]. The possibility that in some forms of urticaria proteases of the complement, kinin, and clotting or fibrinolytic systems are activated to generate vasoactive mediators encouraged us to examine the effects of warfarin in chronic idiopathic urticaria.

We first performed an open study of eight patients with treatment resistant urticaria who appeared to show significant clinical benefit. We then performed a double-blind placebo-controlled cross-over study on three of these patients and confirmed a major therapeutic response. To explore the underlying mechanism, patients were challenged with mast cell degranulating agents: compound 48/80 and histamine both on and off warfarin.

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Materials and methods

Open study

Initially eight patients with a clinical diagnosis of angioedema and chronic idiopathic urticaria without physical precipitating factors or systemic features were studied because their disease was resistant to full dosage of antihistamines. Urticarial vasculitis was not formally excluded by biopsy. All drugs including antihistamines were stopped 1 week prior to the trial. They were asked to assess their global symptoms on a daily basis using a 20-cm linear visual analogue scale where 0 = no symptoms and 20 = worst symptoms ever experienced. Global scores represented general disease activity and well-being. Mean scores were obtained by measuring the actual distance from the origin to the point marked on the scale by the patient. A new scale was used each day and the patients brought all the scales with them for weekly review. The pretreatment assessment period lasted for 3 months after which each patient was anticoagulated with warfarin (there were no clinical contraindications) to achieve an International normalized ratio (INR) between 2.0 and 2.5. Patients were assessed for a further 3 months on treatment and the relative visual analogue scores compared.

After a washout period where the INR returned to normal there was a further assessment of 2 months without treatment. Visual analogue scores were analysed with the Wilcoxon rank sum test as the data derived from the visual analogue scores was not an interval or ratio scale.

Effect of warfarin on response to histamine and compound 48/80

Histamine in doses of 15.6, 62.5, 250, 1000, 4000, and 16000 ng and saline control was injected intradermally into the volar forearm of patients. Weal diameter, skin fold thickness, determined by Harpenden callipers, and erythema, measured with a reflectance meter (Diastron) were compared whilst the patients were fully anticoagulated (INR 2.0–2.5) with warfarin and off warfarin with a normal INR. All patients were off antihistamine treatment for one week prior to challenge. Similarly the same subjects were challenged on and off warfarin with 5, 50, 500, 5000, and 50 000 ng of compound 48/80. Significance was determined with Students paired *t*-test.

Double-blind placebo-controlled study

Three patients from the open study showed dramatic clinical improvement in their symptoms. To confirm that this was a real effect due to therapy, a double-blind placebo-controlled trial was performed. The three patients described below had been shown to have a stable INR on their individual warfarin doses. In conjunction with the pharmacy department at the Royal Liverpool Hospital each patient had their daily individual warfarin dose put into one gelatine capsule. A placebo capsule, identical in appearance, was also provided and the patient took either according to a protocol held by the pharmacy. The trial was conducted in a double-blind placebo-controlled fashion with the pharmacy acting as the third party unblinded dispenser. Patients were randomly allocated to a series of four bottles of capsules — two active and two placebo which they could encounter in any order. There were enough capsules in each bottle for one month's supply taking one capsule a day.

Over the ensuing four months patients were asked to complete weekly 20 cm visual analogue scales to assess their angio-oedema and pruritus. Urticarial lesion number was not assessed. A weeks washout period was given after each change of treatment to allow for levels of warfarin to reach the therapeutic range or to allow levels to fall back to the normal range before scores were taken. Weekly blood for INR measurements were taken irrespective of treatment and were sent to an independent observer blinded to the protocol and treatment to ensure anticoagulation remained within safe limits. Patients were also examined weekly for clinical signs of disease activity and complications of warfarin treatment, but global scores by the examining physician were not made. At the end of the trial the code was broken and responses were compared with treatment groups. The data from the visual analogue scores were analysed statistically by use of the Wilcoxon rank sum test.

In an attempt to characterize this group of patients we performed additional tests. Whilst off all treatment for at least 1 week all patients were inoculated with autologous pretreatment serum as previously described to look for the presence of serum-derived mast cell degranulating factors [3].

Patients

Mr TW a previously fit 38-year-old man presented with a 3-year history of almost daily recurrent facial swelling especially around the eyes and frequent severe urticarial swelling on the body. Individual lesions would last for up to 24 h and fade without trace. There was no family history of urticaria or angio-oedema. He had tried many antihistamines unsuccessfully in standard and high dose and for the previous 2 months a combination of Cimetidine 400 mg b.d. and Loratidine 10 mg o.d. with no benefit. The urticaria was unrelated to any physical factors and all investigations including C1 esterase inhibitor levels and complement levels were normal. Initially he was admitted to hospital for an unsuccessful trial of a strict exclusion diet. Subsequently he was started on warfarin as described and he improved dramatically. Through trial and error it was found

that when his INR (normal = 1.0) fell below 2.0 his urticaria would flare but above this level he would remain virtually symptom free. He has now been controlled on 6 mg warfarin with an INR between 2 and 2.5 for the last 2 years with severe flares of his facial swelling/urticaria should his INR fall substantially. He has suffered no warfarin-related side effects. He agreed to take part in the double-blind placebo-controlled trial.

Mrs KD a 38-year-old lady had suffered from angio-oedema and urticaria for 5 years and during this time she was never completely free of lesions. Urticarial lesions occurred on any area of the body, unrelated to physical stimuli, would last for about 12 h and disappear. She was not helped at all by standard dose and even high dose (Loratidine 30 mg/day) antihistamines and she was otherwise well on no drugs. Routine blood tests, complement and C1 esterase inhibitor levels were normal. She was started on warfarin as a therapeutic challenge. Her symptoms quickly diminished so that by week 2 she was completely free of any lesions. She was stabilized on a steady warfarin dose and she agreed to take part in the double-blind placebo-controlled trial.

Mrs PQ a 54-year-old woman presented with a 3-year history of almost constant crops of urticarial weals on the body and recurrent pruritic facial swelling involving her eyes and mouth. Standard dose antihistamines coupled with cimetidine 800 mg per day limited the attacks to 3–4 per week but she still felt that this was intolerable. She was otherwise well, on no drugs and there was no obvious relationship with physical stimuli.

She was commenced on warfarin and her antihistamines were stopped. As her INR increased she slowly improved and she found that if her INR rose above 3.0 she was completely symptom free. However she developed a sub-conjunctival haemorrhage when her INR was 3.7 and whilst she subsequently had an INR between 2.0 and 2.5 her symptoms were reduced but tolerable. This necessitated warfarin 2 mg per day and at this point she agreed to enter the double-blind placebo-controlled trial.

Results

Open study

Six of the eight patients showed a good clinical response whilst on warfarin, two showed no clinical response. Overall using results from all eight patients in the open trial the benefit derived from warfarin was significant – mean visual analogue score of global symptoms before treatment 14.5 (SD 6.5); mean visual analogue score on treatment: 4.5 (SD 7.9). ($P = 0.017$ 96.1% CI −16 −3 Wilcoxon rank sum test).

There was no significant difference in cutaneous skin fold thickness, weal diameter or erythema measured by the reflectance meter to either histamine or compound 48/80 on or off warfarin. For example when comparing weal diameter 10 min after cutaneous challenge with histamine on and off warfarin results were not significantly different: $P = 0.06$ (Students paired t-test) see Fig. 1. After challenge with compound 48/80 there was no significant difference in weal diameter at 10 min: $P = 0.3$ (Students paired t-test) see Fig. 2.

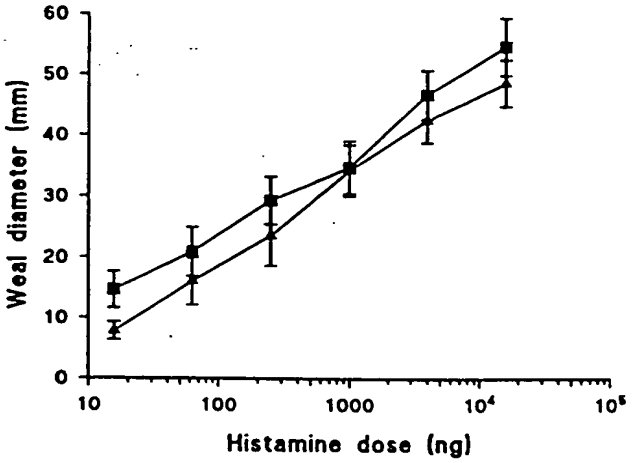

Fig. 1. Effect of warfarin on histamine weal diameter ($n = 8$). Off warfarin (■); on warfarin (▲).

Double-blind placebo-controlled study

Comparison of visual analogue results for angio-oedema on active and placebo treatment showed a significant benefit

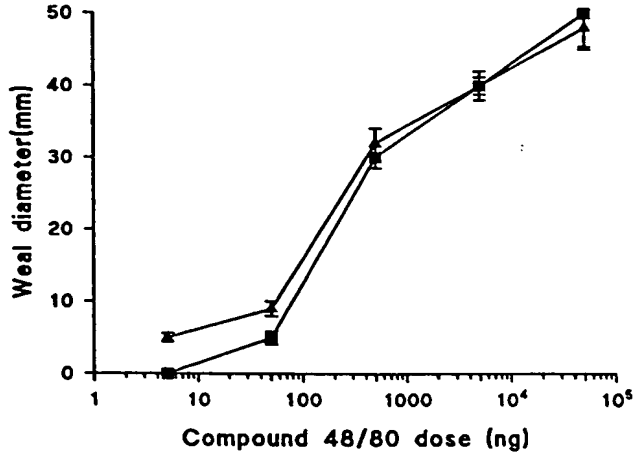

Fig. 2. Effect of warfarin on compound 48/80 weal diameter ($n = 8$). Off warfarin (■); on warfarin (▲).

while on warfarin: mean score on placebo, i.e. the two periods off active treatment was 17.67 whereas mean score on warfarin, i.e. the two periods on active treatment was 5.02 ($P = 0.031$ 96.9% CI−18–5.8 Wilcoxon rank sum test). Similarly, pruritus was greatly reduced: mean values of 16.97 for placebo and 5.05 for active treatment. ($P = 0.031$ 96.9% CI−21.6–6.7 Wilcoxon rank sum test). This confirmed a statistically significant benefit of warfarin treatment both for the angio-oedema and pruritus aspects of the condition.

In all three patients injection of autologous serum gave responses indistinguishable from saline control.

Discussion

The possibility that some patients with chronic idiopathic urticaria would derive clinical benefit from warfarin was originally suggested by Ryan [4] and supported clinically with anecdotal evidence [1,5]. Evidence supporting this was obtained in our open study in which six of eight patients with antihistamine resistant chronic idiopathic urticaria showed clinical benefit. However since chronic idiopathic urticaria is often a variable condition, showing periods of reduced activity or even spontaneous remission we felt it necessary to confirm this was a real therapeutic effect. Therefore a randomized placebo-controlled double-blind trial was performed on three of the patients who showed the most complete resolution of symptoms during the open study. This suggested that in these patients there was a significant beneficial effect of warfarin treatment. As shown with the formal challenge with histamine and compound 48/80, the effects of warfarin were not due to modification of responses to histamine and other mast cell mediators responsible for the acute weal and flare.

The known actions of warfarin are to reduce protein C concentrations and inhibit synthesis of vitamin K-dependent proteins in the clotting cascade (prothrombin and factors VII, IX and X). Warfarin acts as a competitive inhibitor of vitamin K and during the carboxylation of the precursors of these factors, vitamin K is converted to its inactive oxide and then metabolized back to its active form. Warfarin prevents this reconversion. The possibility that activation of clotting or fibrinolytic pathways as a mechanism in angioedema or urticaria was suggested by Ryan. He postulated that plasmin may contribute to the development of urticaria by removing the 'fibrin film wall', by activating complement and by increasing production of fibrin degradation products. However Smith *et al.* provided evidence against the involvement of plasmin [6].

The protein C/S anticoagulant pathway has been proposed to be a common link between coagulation and inflammation and an endothelial cell protein C receptor, modulated by inflammatory cytokines may play a part in this [7]. Activated protein C up-regulates interleukins 6 and 8 and may block neutrophil activation [8]. Warfarin inhibition of thrombin production also contributes to the anti-inflammatory action as in addition to short-term endothelial activation via P-selectin and platelet activating factor release stimulating early neutrophil adhesion and activation, thrombin induces E-selectin and interleukin 8 secretion in human vascular endothelium, facilitating a long acting pro-inflammatory response with neutrophil activation and extravasation [9]. There is convincing evidence that adhesion molecule expression is an important early event in chronic idiopathic urticaria and delayed pressure urticaria facilitating neutrophil infiltration of tissue [10]. Downregulation of these molecules by warfarin may impair vascular endothelial activation and lead to clinical improvement. It has been suggested that differential endothelial adhesion molecule expression may contribute to the pathogenesis of fleeting vs persistent weals [11] and it is of interest that in our patients the clinical impression was of a tendancy for benefit to be maximal against persistent angio-oedematous lesions rather than fleeting weals. This may indicate that warfarin preferentially downregulates certain adhesion molecules important in sustained urticarial/angio-oedema reactions.

Another possibility is that warfarin may modify effects of the proteases in the complement or kinin generating cascades. These processes are important in C1 esterase inhibitor deficiency when activation of C1 generates small vasoactive peptides resulting in vasodilatation and oedema. Also immune/allergic reactions can activate the kallikrein-mediated generation of kinins. One inhibitor of kinin production has been tried successfully in chronic urticaria (Trasylol) [10]. Trasylol inhibits certain proteolytic enzymes including kallikrein—an important kinin-derived from circulating prekallikrein. In high doses Trasylol suppresses C1 esterase and inactivates kallikrein precursors. This is helpful in hereditary C1 esterase inhibitor deficiency which gives rise to angioedema. Pre-kallikrein is activated by a variety of factors including factor XIIa and plasmin. One can easily hypothesize therefore that warfarin may inhibit plasmin activity thereby reducing activation of kallikrein and lowering the tendency to increased vessel permeability, tissue oedema and thus, urticaria. However, there is no evidence of raised kinin levels in urticaria or of low levels of endogenous inhibitors so the mechanism of action remains obscure. There is no doubt however, that our three patients derived and continue to have considerable benefit from the drug. They may represent a small subset of patients with chronic urticaria who respond favourably to this treatment though the mechanism is unknown. However we could not identify any features in these patients that would allow prediction of a good response to warfarin. In particular we could not detect the presence of mast cell degranulating factors in autologous serum in these patients, so this subset appears

not to have the anti-IgE receptor antibody. Further studies are required with larger numbers to determine the characteristics of those patients who do respond. Effects of warfarin on mast cell derived proteases, and the activation of platelets and leucocytes are potential targets. This may provide clues to the mechanism of the weal induction in these patients. If warfarin were to be used in the treatment of angio-oedema/urticaria, then its use should be limited to cases were conventional therapy has failed as the incidence of major haemorrhage is approximately 7% [12], although risk can obviously be minimized by avoiding anticoagulation in high risk cases such as alcohol abuse, chronic renal insufficiency and previous gastro-intestinal haemorrhage.

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Systemic therapy with *griseofulvin* is more effective for moccasin and vesicular bullous disease, and is followed by long-term topical therapy with the azoles and allylamines. Itraconazole, fluconazole, and oral terbinafine combined with a topical azole or terbinafine may replace griseofulvin therapy in the future.

Onychomycosis. Fungal infection of the nails is most frequently caused by dermatophytes but also can be caused by molds and *Candida.* Mixed infections are common. The nail must be cultured prior to therapy, since 30% of nail problems that appear clinically to be onychomycosis are actually due to psoriasis or another dystrophic nail condition (Achten and Wanet-Rouard, 1978). Onychomycosis serves as a reservoir for dermatophytes and contributes to treatment failure and recurrence of tinea pedis.

Oral therapy is necessary for onychomycosis, although the agents currently available, griseofulvin and ketaconazole, have limited efficacy. Treatment of onychomycosis of toenails with griseofulvin for 12 to 18 months produces a cure rate of 50% and a relapse rate of 50% after 1 year (Davies *et al.,* 1967). Results with ketaconazole are equally disappointing, and there is the additional worry of hepatotoxicity. Terbinafine, itraconazole, and fluconazole offer significant potential advantages. They quickly produce high drug levels in the nail, which persist after therapy is discontinued. Additional advantages include a broader spectrum of coverage with itraconazole and fluconazole and few drug interactions with terbinafine. Cure rates of 75% and greater have been achieved with all three drugs, with a shorter duration of treatment than for standard therapy (Gupta *et al.,* 1994a, 1994b). Intermittent regimens with itraconazole (1 week per month) and fluconazole (1 day per week) are undergoing evaluation.

Antiviral Agents

The armamentarium against viral infections unfortunately remains small. The major antiviral drug, *acyclovir,* frequently is used to treat cutaneous herpes simplex, herpes zoster, and chickenpox. The approval of *famciclovir,* a prodrug of penciclovir, and the potential approval of *valacyclovir,* a prodrug of acyclovir, may decrease the length of postherpetic neuralgia in patients. Intralesional injection of interferon alfa-2b is administered for condylomata acuminata. Improvement of psoriasis in AIDS patients with oral zidovudine has been reported. These drug are discussed in Chapter 50.

ANTIHISTAMINES

Histamine is present in mast cells, basophils, and platelets. After release, histamine binds to both H_1 and H_2 receptors in cutaneous vessels, although cutaneous injection of H_1 receptor agonists causes itching, whereas injection of H_2 agonists does not. Complete blockade of H_1 receptors does not totally relieve itching, and some studies suggest that combinations of H_1 and H_2 receptor blockers may be superior to H_1 blockers alone (Bleehen *et al.,* 1987). Older H_1 receptor antagonists have some anticholinergic activity and are sedating. Newer H_1-type antihistamines (*terfenadine, astemizole,* and *loratadine*) lack anticholinergic side effects and are nonsedating, largely because they do not cross the blood-brain barrier. *Cetirizine, acrivastine,* and *temelastine* currently are undergoing review by the FDA or are in clinical trials. H_2 receptor blockers include cimetidine, ranitidine, famotidine, and nizatidine. Besides their use in combination with H_1 receptor blockers for pruritus, the H_2 receptor blockers have immunomodulating effects and have been used in children to treat warts (Orlow and Paller, 1993). Tricyclic antidepressants act on both H_1 and H_2 receptors and have been used to treat pruritus and urticaria.

Antihistamines are frequently used in dermatology to treat pruritus due to urticaria, atopic dermatitis, contact dermatitis, psoriasis, and many other conditions. The newer, nonsedating H_1 receptor blockers are as effective as older H_1 blockers such as hydroxyzine and do not cause tachyphylaxis (Monroe, 1993). Nonsedating antihistamines should not be coadministered with medications that inhibit cytochrome P450 activity, such as ketoconazole or erythromycin, because drug interactions have occasionally been associated with cardiac arrhythmias.

The pharmacology of histamine antagonists is covered in detail in Chapter 25.

TOPICAL ANTIPSORIASIS DRUGS

Psoriasis is a chronic scaling skin eruption characterized by keratinocyte hyperproliferation. It affects 1% of the population of the United States and has a genetic basis. While there is no cure, multiple therapies exist with various modes of delivery (*see* Figure 64–1). Corticosteroids (discussed previously), calcipotriene, and anthralin are topical therapies reserved for localized disease.

Calcipotriene

Calcipotriene (DOVONEX), a vitamin D analog, was approved for the topical treatment of psoriasis in 1994. Chance observation of improvement of psoriasis in an osteoporotic patient receiving an oral derivative of 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2$D], the hormonally active

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to replace prophylactic immunisation. This shows ignorance of the principles of immunisation, one of the greatest success stories of medicine. Because we are host to a plethora of microbes which undergo constant mutation, frequently giving rise to pathogenic strains, we have immunity systems. These have evolved, by selection of reproductive advantage, to prevent the extinction of Homo sapiens by pestilence. The system makes us all different in immunological reactivity, exemplified by our rejection of allografts. When a new pathogen arises, its effects on us range from subclinical infection, through illness of varying severity, to death.

Both infection and immunisation lead to occasional autoimmune diseases, due to development of forbidden clones of lymphocytes which accidentally cross-react with a host antigen in mistake for a microbial one. The autoimmune diseases are potentially preventable by immunisations with vaccines which lack the host-cross-reactive antigens. This is being pioneered by Kehoe[1], who is developing a vaccine for rheumatic fever which lacks the host-cross-reactive antigens. Success in this research will save our vulnerable Maori children from rheumatic fever.

If measles immunisation is stopped, some children (particularly those with Maori type H genes)[2] will die of measles and some, like my sister-in-law, Romula Macfarlane, will die of autoimmune encephalomyelitis, which is 700 times more common after measles infection than after measles immunisation.[3,4] The argument applies to the other infectious diseases, including poliomyelitis where immunisation has abolished the previous tragic deaths and paralyses. Far from needing less immunisations, we need more, including new ones against AIDS, rheumatic fever, the other autoimmune diseases and the so-called "trivial" virus infections (Coxsackie, echo, adeno).

If measles immunisation is not lasting indefinitely, it simply needs to be repeated. Apart from immunisation's wonderful benefit in saving our loved ones from illness and death, it is the epitome of "cost effective" medicine.

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Skin reactions and terfenadine

Terfenadine is an H_1 receptor antagonist which is structurally dissimilar from other conventional antihistamines.[1] Along with other newer antihistamines (astemizole, loratadine and cetirizine), terfenadine has gained widespread popularity due to the lack of sedation as a side effect[2]. This group of antihistamines is nonsedating because they are lipophobic and hence do not readily cross the blood-brain barrier.[2] Serious cardiac arrhythmias have been associated with terfenadine and astemizole either in overdose or with concomitant administration of macrolide antibiotics or imidazole antibiotics.[3] Apart from this, the side effect profile of antihistamine medicines is generally of a minor nature.[3] Terfenadine has previously been associated with skin reactions, albeit rarely.[4,5] We present a case of terfenadine associated skin reaction.

A 53 year old woman was admitted with a 6 day history of generalised urticarial pruritic rash, especially the trunk and proximal parts of her limbs, itchy eyes and throat and some mild lip and periorbital swelling. She had a previous history of allergy to penicillins, erythromycin, some plant and grass species, and cats. This patient had suffered from a bee sting approximately 1 month previously and another bee sting 1 week prior to admission. Current medication history consisted of conjugated equine oestrogen tablets (Premarin) for 4–6 weeks, and terfenadine 60 mg twice daily commenced 4–7 days prior to the rash. These were hormone replacement therapy and selftreatment for rhinorrhoea respectively.

Treatment with intravenous hydrocortisone and oral promethazine brought little relief. After 2 days, treatment with terfenadine 60 mg twice daily was reintroduced, resulting in worsening of her rash and more swelling. Terfenadine was discontinued. The regimen was changed to loratadine, ranitidine and ketotifen with resolution of her symptoms over a 12 hour period.

Results of investigations showed raised acute phase protein (C-reactive protein = 66 mg/L), but were otherwise unremarkable including normal eosinophil count and C_4 level.

Whilst an anaphylactic reaction has been reported for intravenous administration of conjugated oestrogens,[6] we are unaware of reports of skin reactions to this medication.

Prior to discharge further inquiry revealed that she had had a previous hospital admission for an allergic reaction consisting of rash and painful joints. This had been attributed to Benadryl cough medicine, a proprietary preparation containing the antihistamine diphenhydramine and an expectorant, ammonium citrate.

The latent period between first intake of terfenadine and the onset of skin reactions is reported to be between three and seven days.[4] Based upon the temporal relationship between terfenadine administration and onset of rash, and the worsening of symptoms on rechallenge, we deduce that the most likely cause for this patient's hypersensitivity reaction was terfenadine.

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The potential adverse effects of soybean phytoestrogens in infant feeding

It is well established that soybean products contain the phytoestrogens daidzein and genistein.[1-3] We have measured the levels of these compounds in several soy-based infant formulas available in New Zealand. The quantities recommended by manufacturers for infant feeding provide an intake (per kg body weight) of approximately three to five times as much daidzein and genistein than amounts which disrupt the menstrual cycle when fed to premenopausal women.[4] Exposure to phytoestrogens during soy-formula feeding is cause for considerable concern given the greater susceptibility of neonates to oestrogens and the likely duration of exposure through infancy.

The soy phytoestrogens act by (1) inhibiting the enzyme 17-ß-hyroxysteroid oxidoreductase, type 1, which converts the relatively impotent oestrone to the much more potent oestradiol; (2) occupying the oestrogen receptor, thus acting as antagonists to the naturally-produced oestradiol, inhibiting its effects (this behaviour is similar to that of another oestrogen agonist-antagonist, tamoxifen).[4] The consequent reduction in oestrogenic action appears to have a useful prophylactic effect against many oestrogen-dependent disorders in adults, including mammary and prostatic tumours.[5] However, the same effect is deleterious in infants. Considerable research has shown that adequate oestradiol is necessary for the imprinting and development of many physical, physiological and behavioural characteristics during the neonatal period and infancy.[6-7] Any decrease in the amount of oestradiol available is potentially harmful. Unfortunately, no specific research has investigated the effects of soy on these characteristics in the human infant, although it has been shown that phytoestrogens are absorbed similarly in infants and adults.[8]

It has been claimed that soy-formulas are unlikely to cause harm to infants because they have been used for years without adverse reports (O'Regan, personal communications, 1 February 1995). However, another oestrogen, diethylstilbestrol (DES), was administered extensively to women over three decades before the spectrum of harmful effects appeared, some manifesting themselves only when DES offspring reached adulthood.[9] Furthermore, although many women have consumed soy products without reports of problems, when a definitive experiment was conducted, consumption of 60 g of soy protein per day for 1 month disrupted the menstrual cycle during, and for up to 3 months after, administration.[4] Therefore the argument that no adverse effects were observed, therefore none occurred, is incogent. It is also plausible that harmful effects have occurred but have not been linked to soy consumption.

Other researchers have similar concerns about exposing young infants to phytoestrogens. The introductory paper presented by the USFDA Department of Health at a recent phytoestrogen conference notes 'phytoestrogens have some of the same capabilities to induce developmental toxicity as do other estrogens' and 'given the DES tragedy, it would be foolish to ignore the possibility that some phytoestrogens constitute a developmental hazard'.[10]

The New Zealand Ministry of Health has advised that parents 'continue to feed their infants soy-based milk formula if they have been advised to do so by their health specialists' (O'Regan, personal communications, 29 March 1995). However, soyformulas are available at supermarkets enabling parents to choose them without medical advice. It would be prudent for general sales of soy-formulas to be stopped. Failing this there is a need for information to be made available to both physicians and

Loratadine in the Treatment of Urticaria

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ABSTRACT

Urticaria is a common skin disease, which, in its chronic form, is a very disturbing condition. Because histamine is the best-documented chemical mediator of urticaria, histamine$_1$-antagonists are the mainstay of therapy. First-generation antihistamines are limited by their tendency to produce sedation and anticholinergic side effects. Most of the newer second-generation antihistamines compare well with the earlier agents in efficacy but are not limited by the same adverse side effects. Loratadine may be distinguished from other second-generation antihistamines by its pharmacodynamic profile, as well as its tolerability and safety. ***Key words:*** loratadine, antihistamines, urticaria.

INTRODUCTION

Although not life-threatening, chronic urticaria (hives) has been described as one of the most disturbing problems in clinical medicine.[1] In addition to causing embarrassment and discomfort, it may produce sleep, social, emotional, and cosmetic problems. Lost production and school days have negative economic sequelae. Health care dollars are often wasted on repeated physician visits, expensive diagnostic testing, and unsatisfactory therapies.

Epidemiology of Urticaria

Urticaria, one of the 20 most common skin diseases,[2] is characterized by intense itching and numerous, usually transient, erythematous skin lesions that can form on any area of the body. Each lesion consists of a raised portion or wheal, surrounded by a halo or flare. In acute urticaria, the symptoms disappear within 6 weeks. In patients with chronic urticaria, symptoms may last more than 6 weeks. Angioedema, a nonpruritic syndrome associated with swelling in deeper parts of the skin or subcutaneous tissues, often occurs in combination with urticaria and is

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believed to be caused by the same pathogenic mechanisms. Approximately 25% of the populations of the United States and United Kingdom are believed to be affected by urticaria/angioedema at some time in their lives. In addition, 25% of all urticarial patients have chronic idiopathic urticaria.[2,3]

Etiology of Urticaria

In addition to duration, urticarias are also classified according to the precipitating stimuli, if known. Mahmood[4] suggested that there are six "I's" of etiologic agents for urticaria, including ingestants (foods), injectants (drugs), insect stings, inhalants, infections, and internal diseases. Foods and drugs are believed to act through both immunologic and nonimmunologic mechanisms. Foods are common causes of acute urticaria but are believed to actually cause very few (perhaps 1.4% to 2.1%) cases of chronic urticaria.[5] About 15% of urticarias are caused by physical stimuli, including pressure (dermographic), heat, cold, light, vibration, exercise (cholinergic), and water.[6] Even with diligent review of patient history and challenge testing, for more than 75% of chronic urticarial patients the cause remains undetermined, and the disorder is considered idiopathic.

The Role of Histamine in Urticaria

While it is beyond the scope of this paper to review the documentation for the role of histamine in the pathogenesis of urticaria, the salient evidence includes increased concentrations of histamine in urticarial skin and tissue fluids[7–9] and the clinical response of urticaria to antihistamine therapy.[10] Histopathologically, urticaria is characterized by increased concentration of mast cells,[11] which are the main source of histamine in the skin.[12] Experimental injection of histamine subcutaneously replicates the key components of the urticarial reaction, including localized erythema resulting from vasodilation, wheal formation from edema secondary to increased vascular permeability, and pruritus. Pretreatment with histamine$_1$ (H_1)-antagonists can prevent the onset of these symptoms.[12] In short, the understanding that histamine release from mast cells is an essential component of the pathophysiology of urticaria led to the introduction and use of antihistamines as treatment for urticaria.

Treatment of Urticaria

The pruritic, vasodilatory, and vasopermeable actions of histamine associated with urticaria are mediated through H_1-receptors. Although the classic or first-generation H_1-antagonists (eg, hydroxyzine, chlorpheniramine, diphenhydramine, and cyproheptadine) and cetirizine preferentially inhibit H_1- rather than H_2- or H_3-receptors, they may also activate muscarinic, cholinergic, serotonergic, or alpha-adrenergic receptors, leading to unwanted side effects.[10]

The second-generation antihistamines selectively antagonize H_1-receptors, and their inability to cross the blood-brain barrier due to lipid insolubility precludes central nervous system (CNS) sedation (excluding cetirizine). Thus most newer antihistamines, including astemizole, loratadine, and terfenadine, compare well with the earlier agents in efficacy but are not limited by the same adverse side effects. The exception to this is cetirizine, which is sedating compared with placebo

and second-generation antihistamines such as loratadine, but less sedating than the first-generation antihistamines.

In addition to histamine, the release of other mast cell mediators, including kinins, eicosanoids, and neuropeptides, may also be involved in urticaria.[3] In vitro, loratadine has been shown to inhibit the release of histamine and other inflammatory mediators in addition to its H_1-receptor blocking activity.[13,14] There is evidence that the mechanism for the inhibition of mediator release by loratadine occurs via interference with calcium transport across cell membranes.[15]

LORATADINE

Loratadine may be favorably distinguished from other second-generation antihistamines by its pharmacodynamic profile and its tolerability and safety.

Pharmacodynamics

Loratadine's clinical utility for the treatment of urticaria is at least partly attributed to its quick onset and sustained duration of action. Loratadine (10 mg) is rapidly absorbed after oral administration and reaches peak plasma levels within 1 to 2 hours.[16] It undergoes extensive first-pass metabolism in the liver. Loratadine has an elimination half-life of 8 to 11 hours, but its primary, active metabolite (descarboethoxyloratadine) has a half-life of 28 hours, allowing once-a-day dosing.[17–19] Steady-state levels are achieved by day 5 of chronic oral dosing.

Wheal and Flare Studies

Although the histamine-induced wheal and flare reaction does not necessarily predict the relative clinical efficacy of antihistamines, the intradermal injection of histamine to produce wheal and flare reactions is an experimental method used to simulate urticaria and to evaluate the antihistaminic activity of drugs. Single and multiple doses of loratadine suppress the wheal response to intradermal histamine (2 μg) within 1 to 2 hours of oral administration.[20–22] Both the magnitude and duration of wheal suppression by loratadine are dose related. In healthy volunteers, wheal inhibition over a 48-hour period showed a dose-response relationship between 10 and 80 mg.[21] In a single-dose study, loratadine 10 mg suppressed wheal and flare areas 4 to 24 hours after injection of histamine 1 mg/mL, with peak effect at 8 hours after dosing.[23] After daily administration for 7 days, loratadine 10 mg inhibited the wheal and flare reaction to histamine 1 mg/mL for nearly 7 days after discontinuation in adult asthmatic patients.[24]

Antihistaminic activity may persist even after plasma concentrations of drug or metabolites are no longer detectable.[10] A short course of astemizole (10 mg daily) can produce sustained effects, as measured by wheal and flare suppression, for as long as 8 weeks.[25] This property, which distinguishes astemizole from other second-generation antihistamines, may be of particular concern to women of childbearing age who may not want to remain exposed to astemizole for prolonged periods, especially because it is rated pregnancy category C. Loratadine, which is not associated with teratogenicity in animal studies, is rated category B.

The protracted duration of action of antihistamines should also be considered when patients undergo skin testing for urticaria-inducing allergens. To avoid in-

terfering with skin tests, antihistamine therapy with cetirizine (based on half-life calculation) or loratadine should be discontinued for 7 days prior to testing and for 42 days with astemizole.[10]

Clinical Studies

The effectiveness of antihistamines in suppressing histamine-induced skin reactions provides the rationale for their clinical application in urticaria. Hydroxyzine was considered the standard therapy for chronic urticaria, and the efficacy of the newer antihistamines is often compared with that of hydroxyzine.[26] In the clinical studies listed in the table,[1,27–32] loratadine was found to be more effective than placebo, as effective as hydroxyzine, and as effective or more effective than terfenadine.

Loratadine Versus Placebo

In a double-masked, placebo-controlled trial involving 153 patients, Monroe et al[29] found that loratadine 10 mg once daily improved symptoms of chronic urticaria, according to patient and physician evaluations, within 1 week after beginning the 4-week trial. By the last patient evaluation, the loratadine-treated patients reported a 71% improvement in total symptom scores compared with a 43% improvement in the placebo-treated group ($P < 0.01$). Significantly more ($P < 0.01$) placebo-treated patients than loratadine-

Table. Clinical studies of loratadine in patients with chronic idiopathic urticaria.

Study	No. of Patients	Results
Belaich et al[1]	172	Loratadine 10 mg more effective than placebo, $P < 0.01$ Loratadine 10 mg more effective than terfenadine 60 mg BID, P = NS Terfenadine 60 mg BID more effective than placebo, $P < 0.01$
Bernstein and Bernstein[27]	30	Loratadine 10 mg QD more effective than placebo, $P < 0.01$
Guerra et al[28]	116	Loratadine 10 mg more effective than placebo, $P < 0.01$ Loratadine 10 mg more effective than cetirizine 10 mg, P = NS Cetirizine 10 mg more effective than placebo, $P < 0.01$
Monroe et al[29]	153	Loratadine 10 mg more effective than placebo, $P < 0.01$
Monroe[30]	18	Loratadine 10 mg equally effective as hydroxyzine 25 mg TID and more effective than placebo, $P < 0.01$
Monroe et al[31]	172	Loratadine 10 mg equally effective as hydroxyzine 25 mg TID and more effective than placebo, $P < 0.01$
Shareeah[32]	30	Loratadine 10 mg more effective than terfenadine 60 mg BID, $P < 0.05$

BID = twice daily; QD = every day; TID = three times daily.

treated patients discontinued treatment early because of treatment failure.

Loratadine Versus Hydroxyzine

In comparison to other drugs, loratadine 10 mg daily was as effective as hydroxyzine 25 mg three times a day in a 1-week, double-masked, placebo-controlled study of 18 patients with chronic urticaria.[30] The total symptom scores improved 43% with loratadine and 47% with hydroxyzine (P = NS), and the improvement with both drugs was significantly greater than the 0% improvement seen with placebo ($P < 0.01$). As would be expected, the hydroxyzine-treated patients experienced significantly more sedation than those receiving loratadine.

A larger, 4-week (optional 12-week), double-masked, placebo-controlled study verified the similar efficacy of loratadine, 10 mg once daily, and hydroxyzine, 25 mg three times daily, in 172 patients with chronic idiopathic urticaria.[31] At the end of the study, approximately two thirds of the patients in each active treatment group achieved marked or complete relief of symptoms. No statistically significant difference was noted between the two active treatment groups at any evaluation period.

Loratadine Versus Other Second-Generation Antihistamines

Clinical studies comparing the second-generation antihistamines with each other have generally shown no statistically significant differences in clinical efficacy among the new agents. However, some studies do demonstrate clinical differences in efficacy, onset of action, and adverse events.

In a double-masked, placebo-controlled study involving 172 patients,[1] loratadine 10 mg once daily for 4 weeks improved symptom scores 56% versus terfenadine 60 mg twice daily, which improved symptom scores 37%. Although loratadine was clinically superior, the differences were not statistically significant. Loratadine and terfenadine were significantly better than placebo ($P < 0.01$). Approximately twice as many terfenadine-treated patients discontinued therapy because of treatment failure than loratadine-treated patients. Again, the difference was not statistically significant.

Another study[32] compared loratadine (10 mg daily) and terfenadine (60 mg twice daily) in a nonplacebo-controlled design and showed a clinical superiority for loratadine ($P < 0.05$).

In a 4-week, double-masked study of 116 patients with chronic urticaria, Guerra et al[28] showed that loratadine (10 mg daily) had a more rapid onset of action (3 days) than cetirizine (10 mg daily). By day 14 and through the completion of the study, loratadine remained more effective than cetirizine in controlling urticarial symptoms, although the differences between groups were not significant. Loratadine and cetirizine were significantly more effective than placebo ($P < 0.01$). The frequency of side effects was equivalent in the loratadine and placebo groups (15.8%), but was nearly doubled in the cetirizine group (27.5%).

In a study comparing loratadine (10 mg daily) with astemizole (10 mg daily) over a 4-week period,[33] the first detectable treatment effect on the disappearance of wheals, erythema, or pruritus occurred noticeably earlier in the loratadine group. The median onset of action for loratadine was 3 hours after the *first* dose compared with 2 to 3 hours after the *third* dose for astemizole ($P < 0.01$). By the end of the third day, 20% of the astemizole group still had not experienced symptom relief.

Tolerability

Loratadine is generally viewed as a safe and well-tolerated medication in children, adults, and the elderly. Data obtained from more than 55,000 patients who participated in controlled and open clinical trials and from postmarketing surveillance data in 1992 representing loratadine's use in approximately 9 million patients indicated a low incidence of spontaneously reported adverse reactions to loratadine (5.9/10,000 patient years).[34] The most frequent adverse effects included headache, fatigue, dizziness, and nausea. The following sections will show that, unlike some other second-generation antihistamines, loratadine does not produce sedation, cardiac toxicity, or weight gain.

Sedation

Many clinicians currently believe that most of the second-generation H_1-antagonists are more tolerable and safer than the first-generation drugs. For instance, the newer agents usually produce less somnolence and other negative CNS effects and do not potentiate the adverse CNS effects of alcohol and other CNS depressants.[35]

In clinical studies, loratadine has been shown to be free of the sedative effects produced by classic antihistamines. For example, diphenhydramine 50 mg three times daily for 2 days increased sleepiness and impaired performance efficiency on a battery of psychometric tests (reaction time, vigilance, digit/symbol substitution, symbol copying) in 16 healthy individuals. In contrast, loratadine 10 or 40 mg had no such CNS effects.[36] Adelsberg and D'Amico-Beadon[37] compared loratadine and diphenhydramine and found subjects taking diphenhydramine did poorly on tasks requiring clerical, accounting, or math skills; visual attention; and visual and auditory memory. In contrast, no similar impairments were noted with loratadine or placebo. Monroe et al[31] reported a significantly ($P < 0.01$) higher incidence of sedation with hydroxyzine (49%) than with loratadine (7%) or placebo (3%).

When loratadine was compared with other newer antihistamines, DeRoeck et al[38] noted more sedation with cetirizine or with diphenhydramine than with either placebo or loratadine, as measured by standardized performance and sleep latency tests. In another study,[39] cetirizine 10 mg adversely affected driving performance in a fashion similar to that of alcohol, and its effects were additive with alcohol; in contrast, loratadine 10 mg had no significant adverse effects on driving. In a study of the treatment of allergic rhinitis with either loratadine or cetirizine,[40] somnolence was reported in 9.5% of patients treated with cetirizine compared with 3.6% of patients treated with loratadine. These findings support the conclusion that cetirizine is sedating, although less sedating than first-generation antihistamines, and carries with it the full sedation precautions found with sedating antihistamines. The prescribing information for cetirizine reads as follows: "Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking Zyrtec*; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of Zyrtec with alcohol or other CNS depressants should be avoided because additional reductions in

*Trademark: Zyrtec™ (cetirizine hydrochloride), Pfizer Inc., New York, New York.

alertness and additional impairment of CNS performance may occur."[41]

These and other studies indicate that an important feature of loratadine is that it does not interfere with daily activities. In a randomized, double-masked study of alertness and performance on a flight simulator, the skills of 40 commercial and military airplane pilots after a single 10-mg dose of loratadine were as good as they were with placebo.[42] The lack of sedative activity of loratadine was also found in clinical trials involving the treatment of other allergic conditions such as seasonal allergic rhinitis.[43,44]

Torsades de Pointes

Two of the second-generation antihistamines, terfenadine and astemizole, can be distinguished from the others by their propensity to cause a potentially life-threatening cardiac arrhythmia, torsades de pointes (TDP).[45,46] These drugs also prolong the QT_c interval (ie, the interval corrected for heart rate) on an electrocardiograph (ECG), and this change is often a diagnostic and predictive marker for TDP. A warning from the US Food and Drug Administration indicated that the cardiac abnormalities with terfenadine and astemizole are usually associated with overdosage, certain drug interactions (eg, with ketoconazole, itraconazole, or erythromycin), or hepatic dysfunction.[47]

Loratadine and cetirizine do not exhibit the adverse cardiac actions described for astemizole and terfenadine.[46,48] For instance, Affrime et al[49] reported in a placebo-controlled study that loratadine produced no changes in the QT_c interval or other ECG changes and no episodes of syncope in humans, even at a dose (40 mg) that significantly exceeded the recommended clinical dose. In guinea pigs, loratadine 30 mg/kg intravenously had no adverse cardiovascular effects, unlike terfenadine 10 mg/kg, which caused arrhythmogenic activity, prolonged QT_c interval, bradycardia, and hypotension.[50] In drug interaction studies, although administration of loratadine with erythromycin, cimetidine, or ketoconazole elevated plasma levels of loratadine and its active metabolite, the combinations produced no ECG changes, sedation, or syncope.[51] It has been suggested that unlike terfenadine or astemizole, loratadine does not block the delayed rectified potassium channel at concentrations up to 10 μmol, and that this is the critical reason loratadine does not produce TDP.[48]

Weight Gain

Increased appetite and weight gain are adverse effects sometimes observed with astemizole therapy. For instance, in a placebo-controlled study of 46 patients with chronic idiopathic urticaria, Kailasam and Mathews[52] reported a mean weight gain during astemizole treatment of 2.2 kg (4.8 lb) over 8 weeks; the maximum weight gain was 5.8 kg (12.8 lb). In a randomized, double-masked study of 167 patients with seasonal allergic rhinitis,[53] patients treated with astemizole 10 mg daily gained more weight than patients treated with loratadine 10 mg daily. The differences in weight gain between the loratadine and astemizole treatment groups were statistically significant at 4, 6, and 8 weeks ($P \leq 0.012$).

Tachyphylaxis

Within days to weeks, first-generation antihistamines occasionally show a significant decline in their clinical effectiveness and ability to inhibit the wheal and flare response; higher doses are necessary

to achieve the same effect. This reduced sensitivity does not occur with astemizole,[54] loratadine,[55] or terfenadine.[56]

OTHER TREATMENTS FOR URTICARIA

When the precipitating agent of urticaria is known, the best treatment is avoidance. For people prone to urticarial outbreaks, attempts should also be made to minimize exposure to factors that may exacerbate urticaria, such as heat, fever, exercise, menstrual changes, emotional stress, and aspirin.[3,4] The nonsedating antihistamines are considered first-line therapy for most urticarias, with the exception of some physical urticarias.[57,58] Because antihistamines are more effective in preventing the actions of histamine than reversing its effects, many clinicians believe that the management of chronic urticaria is best achieved with regular prophylactic doses of antihistamines.[59] Oral corticosteroids are generally reserved for patients with severe disease who do not respond to antihistamines. Other treatments that are occasionally of value in the treatment of urticaria include H_2-receptor antagonists, tricyclic antidepressants, beta-adrenergic agonists, calcium antagonists, cromolyn-like agents, and plasmapheresis.[6,60]

CONCLUSIONS

Loratadine satisfies the criteria for the "ideal H_1-antagonist for regular prophylactic treatment of urticaria" as described by Goldsmith and Dowd[59]: it is orally active, has a rapid onset, requires only once-daily administration, and has minimal unwanted side effects. Although it may not always be the most efficacious second-generation antihistamine for the treatment of urticaria, its effectiveness, combined with its selectivity, safety, and tolerability, distinguishes it from other members of its class and makes it an excellent choice for the treatment of most urticarias.

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